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Radiotherapy

Evidence Update

May 2018

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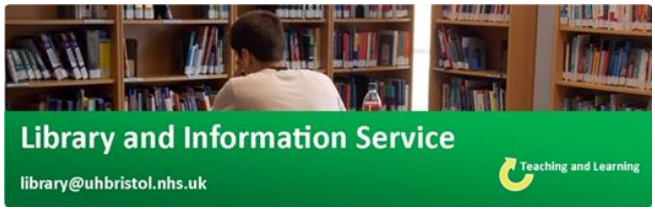

Contents

Current Journals: Tables of Contents

Click on journal title (+ Ctrl) for hyperlink

Journal	Month	Volume	Issue
Radiotherapy and Oncology	May 2018	127	2
International Journal of Radiation Oncology Biology and Physics	July 2018	101	3
Clinical Oncology	June 2018	30	6

If you require full articles please email: library@uhbristol.nhs.uk

Lunchtime Drop-in Sessions

All sessions last one hour

June (12.00-13.00)

7th (Thu) Literature Searching

11th (Mon) Critical Appraisal

20th (Wed) Interpreting Statistics

28th (Thurs) Literature Searching

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Latest Evidence

NICE National Institute for Health and Care Excellence

Low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy - guidance (IPG615)

Source: National Institute for Health and Care Excellence - NICE - 23 May 2018

Evidence-based recommendations on low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy.

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Overview of treatment approaches for hepatocellular carcinoma

Authors: Eddie K Abdalla, MD; Keith E Stuart, MD

Section Editors: Kenneth K Tanabe, MD; Richard M Goldberg, MD

Deputy Editor: Diane MF Savarese, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Nov 16, 2017.

Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization

Authors: Steven A Curley, MD, FACS; Keith E Stuart, MD; Jonathan M Schwartz, MD; Robert L Carithers, Jr, MD; Klaudia U Hunter, MD

Section Editors: Kenneth K Tanabe, MD; Christopher G Willett, MD

Deputy Editor: Diane MF Savarese, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Oct 30, 2017.

Bone metastases in advanced prostate cancer: Management

Authors: A Oliver Sartor, MD; Steven J DiBiase, MD

Section Editors: Nicholas Vogelzang, MD; W Robert Lee, MD, MS, MEd; Jerome P Richie, MD, FACS

Deputy Editor: Michael E Ross, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Jan 15, 2018.

External beam radiation therapy for localized prostate cancer

Authors: Steven J DiBiase, MD; Mack Roach, III, MD

Section Editors: Nicholas Vogelzang, MD; W Robert Lee, MD, MS, MEd; Jerome P Richie, MD, FACS

Deputy Editor: Michael E Ross, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** May 08, 2018.

Radiation therapy in the management of melanoma

Author: Angela M Hong, MBBS, MMed, PhD, FRANZCR

Section Editor: Michael B Atkins, MD

Deputy Editor: Michael E Ross, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** May 07, 2018.

Overview of gastrointestinal toxicity of radiation therapy

Authors: Brian G Czito, MD; Jeffrey J Meyer, MD; Christopher G Willett, MD

Section Editor: Reed E Drews, MD

Deputy Editor: Shilpa Grover, MD, MPH, AGAF

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Apr 11, 2018.

Postoperative radiation therapy in the management of head and neck cancer

Authors: Shruti Jolly, MD; Avraham Eisbruch, MD; Francis P Worden, MD; Richard Smith, MD

Section Editors: Bruce E Brockstein, MD; David M Brizel, MD; Marshall R Posner, MD; Marvin P Fried, MD, FACS

Deputy Editor: Michael E Ross, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Apr 23, 2018.

Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus

Authors: Noah C Choi, MD; Michael K Gibson, MD, PhD, FACP

Section Editors: Richard M Goldberg, MD; Christopher G Willett, MD

Deputy Editor: Diane MF Savarese, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** May 14, 2018.

Royal College of Radiologists

The future of paediatric radiotherapy services [Position statement]

Tuesday 17 April 2018

The Society of Radiographers

Radiographer-led blood product prescribing

22 May, 2018

AUTHOR: LUCY DAVIDSON, SPECIALIST RADIOGRAPHER, CHRISTIE NHS FOUNDATION TRUST

Developing a degree level apprenticeship standard for therapeutic radiography

10 April, 2018

AUTHOR: HAZEL (BAZ) ROGERS, HEAD OF RADIOTHERAPY, LEEDS CANCER CENTRE (THERAPEUTIC RADIOGRAPHER APPRENTICESHIP TRAILBLAZER CHAIR) AND GEMMA BURKE, SENIOR LECTURER, SHEFFIELD HALLAM UNIVERSITY (THERAPEUTIC RADIOGRAPHER APPRENTICESHIP TRAILBLAZER MEMBER)

Institute of Physics and Engineering in Medicine

Conference resources

Adaptive Approaches and Online Monitoring of Radiotherapy Treatment - 25th April 2018, Manchester

Programme	Abstracts	Biographies	Presentations (IPEM Members only)

Heads of Radiotherapy Physics - 5th-6th February 2018, Northampton

Programme	Presentations (IPEM Members only)

Current Awareness Database Articles

Below is a selection of articles recently added to the healthcare databases, grouped in the categories:

- **Liver SABR**
- **Radium 223 - Prostate and breast metastases**

If you would like any of the articles in full text, or if you would like a more focused search on your own topic, please contact us: library@bristol.nhs.uk

Liver SABR

1. Feasibility of split-course stereotactic ablative radiotherapy for oligometastases.

Author(s): Paik, Eun Kyung; Kim, Mi-Sook; Seo, Young-Seok; Jang, Won; Kang, Jin-Kyu; Cho, Chul-Koo; Yoo, Hyung Jun

Source: Japanese journal of clinical oncology; May 2018

Publication Date: May 2018

Publication Type(s): Journal Article

PubMedID: 29722825

Abstract: BackgroundThere is growing interest in the use of stereotactic ablative radiotherapy (SABR) for oligometastases. However, extreme caution should be exercised in treating tumors closely located to organs at risk (OARs) with SABR. To reduce complications, we have applied split-course SABR to oligometastases closely located to OARs or to those being retreated with radiotherapy.MethodsWe retrospectively reviewed the records of patients with oligometastases who were treated with planned split-course SABR between January 2012 and December 2016.ResultsA total of 23 patients with 29 oligometastatic lesions were enrolled. The primary diagnoses were bone and soft tissue cancers in 13 lesions, liver cancers in 12 lesions, and colorectal cancers in four lesions. The median tumor volume was 78 cm3 (range, 4-1781 cm3). The lesions were treated with 1-3 fractions in the first stage of SABR (first SABR), and one or two fractions in the second stage of SABR (second SABR). The time interval between the two stages was about 4 weeks. A partial response was noted in 16 lesions (55%) after the first SABR, and practical reductions in the doses to OARs were observed in the second SABR compared with the first SABR. The 1-, 2- and 3-year local control rates were 92%, 65% and 43%, respectively. No Grade 4 or 5 toxicities were observed during or after treatment.ConclusionSplit-course SABR appeared to be feasible for the treatment of oligometastases closely located to OARs.

2. Ablation of colorectal liver metastases by irreversible electroporation: Final results of the COLDFIRE-2 Trial

Author(s): Vroomen L.; Ruarus A.; Scheffer H.; Van Kuijk C.; Van Den Tol P.; Meijerink M.

Source: Journal of Vascular and Interventional Radiology; Apr 2018; vol. 29 (no. 4)

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract: Purpose: To investigate the safety and efficacy of irreversible electroporation (IRE) for colorectal liver metastases (CRLM) that are contraindicated for surgical resection and thermal ablation because of safety or efficacy concerns. Materials: In this prospective, single-Arm, phase-II trial 40 patients with CRLMs <= 3.5 cm were treated with IRE. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0. Threemonthly 18F-FDG PET-CT, contrast-enhanced CTs and MRIs were made to detect disease progression. Kaplan-Meier estimates were used for survival analysis. Results: IRE was successfully performed in all 40 patients (49 CRLMs). There were no IRE related deaths. There were 10 minor AEs (grade I or II) and nine major complications (seven grade III, two grade IV). After a median follow-up of nine months (range, 0-34 months), eight lesions showed an ablation site recurrence, three were successfully retreated (primary efficacy rate 76%; assisted efficacy rate 85%). Median disease free survival was 4.5 months (95%-CI 2.8-6.1 months); first site of disease recurrence was liver (n = 11), lung (n = 3), liver & lung (n = 11), intestines (n = 2), peritoneal deposits (n = 3), bone (n = 2), and brain (n = 1). Median overall survival was not reached; one-year overall survival was 78%. Conclusions: IRE represents a safe and effective technique for patients with small CRLM (<= 3.5 cm) that are unsuitable for surgery and thermal ablation. Although the outcome regarding local tumor control appears to be promising, the relatively high number of early distant site recurrences should keep us wary. The results mandate the setup of a trial comparing IRE to stereotactic ablative radiotherapy (SABR) for CRLM unsuitable for surgery and thermal ablation (COLDFIRE-3).

3. [Stereotactic body radiotherapy of liver metastasis: early experience].

Author(s): Földi, Gerda; Polgár, Csaba; Zongor, Zsuzsánna; Melles-Bencsik, Barbara; Stelczer, Gábor; Madaras, Balázs; Pintér, Tamás; Jederán, Éva; Lövey, József

Source: Magyar onkologia; Mar 2018; vol. 62 (no. 1); p. 62-67

Publication Date: Mar 2018

Publication Type(s): English Abstract Journal Article

PubMedID: 29570188

Abstract: Recently the prevalence of oligometastatic patients is increasing. A common site of distant spread is the liver. The standard of care is curative surgical resection, however, the resecability rate is only 10-20%. Alternatively, radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) may be used. Stereotactic ablative body radiotherapy (SABRT) makes it possible to deliver curative radiation dose without radiation injury to the healthy liver tissue. We delivered SABRT to three patients with inoperable hepatic metastases. The primary tumors were rectal (2) and lung (1). The dose was 3x20 Gy every other day. We observed one grade 1 side effect. All the metastases showed complete remission and no local recurrence or late side effect occurred during the one year of follow-up. One patient is tumor-free, one has stable disease, in one patient two new hepatic metastases appeared and receives chemo-biological therapy. SABRT of liver metastases is safe and highly effective. It can be expected that in the near future it will become one of the standard treatments of hepatic tumors.

4. Expiration breath-hold stereotactic ablative body radiotherapy for primary liver cancer

Author(s): Welsh B.; Khor R.; Seeley A.; Shelton N.; Harris B.

Source: Journal of Medical Radiation Sciences; Mar 2018; vol. 65 ; p. 28

Publication Date: Mar 2018

Publication Type(s): Conference Abstract

Available at Journal of medical radiation sciences - from Wiley Online Library Free Content - NHS

Available at Journal of medical radiation sciences - from Europe PubMed Central - Open Access

Available at Journal of medical radiation sciences - from PubMed Central

Abstract: Stereotactic ablative body radiotherapy (SABR) has a growing role in the management of hepatocellular carcinoma (HCC), and is technically challenging due to potential motion of the liver and surrounding organs due to respiration. Liver SABR may be delivered during normal free breathing, using an internal target volume (ITV) approach defined from 4DCT. However, delivery during breath-hold significantly reduces respiratory motion and therefore the volume of normal tissue irradiated, potentially decreasing toxicity including radiation induced liver disease. Expiration breath-hold (EBH) for liver patients requires effective com-munication to ensure accurate delivery. High-quality patient education in the use of the Elekta Active Breathing CoordinatorTM (ABC) is essential for successful planning and treatment processes. A planning CT with multi-phase contrast acquisitions in breath-hold and acquisition at treatment of a 'stop-and-go' 3D CBCT over several breath holds can only be achieved with successful collaboration between radiation therapists and the patient. Liver EBH SABR was successfully implemented through collaboration with both international colleagues and institutional medical imaging and radiation oncology departments. High-quality diagnostic imaging in EBH allows for precise target and normal tissue definition. Ultrasound-guided fiducial marker insertion allows for increased confidence in IGRT for liver SABR. The EBH technique has enabled safe and efficient liver SABR delivery, with potential to improve the outcomes for patients undergoing radiotherapy for HCC.

5. Unresectable hepatic PEComa: a rare malignancy treated with stereotactic body radiation therapy (SBRT) followed by complete resection.

Author(s): Kirste, Simon; Kayser, Gian; Zipfel, Anne; Grosu, Anca-Ligia; Brunner, Thomas

Source: Radiation oncology (London, England); Feb 2018; vol. 13 (no. 1); p. 28

Publication Date: Feb 2018

Publication Type(s): Journal Article

PubMedID: 29463266

Available at Radiation Oncology - from BioMed Central

Available at Radiation Oncology - from Europe PubMed Central - Open Access

Available at Radiation Oncology - from EBSCO (MEDLINE Complete)

Available at Radiation Oncology - from PubMed Central

Abstract:BACKGROUNDPerivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors occurring in various anatomic regions. Although diagnostic criteria and treatment management are not established, current treatment options consist of surgery and chemotherapy including mTOR inhibitors. Stereotactic body radiation therapy (SBRT) is a non-invasive ablative treatment which has shown excellent control rates for more common types of unresectable liver tumors and metastases. In this report we present a rare case of PEComa of the liver that was treated by stereotactic radiotherapy followed by resection. Staging and evaluation of treatment response was done by FDG-PET/CT. This case highlights the potential of SBRT as a neoadjuvant treatment even for rare liver malignancies. It is the first case of liver PEComa treated by SBRT and resection.CASE PRESENTATIONA 52-year-old woman presented at an external hospital with abdominal pressure and pain in the right upper abdominal quadrant. A CT scan showed a 700 cm3 liver lesion in segment IV. In repeated biopsy in July 2015 histopathological workup showed a pleomorphic epitheloid tumor with small to medium sized cells expressing vimentin and melan-A while being negative for cytokeratin establishing the diagnosis of PEComa of the liver. To achieve high, ablative doses a stereotactic body radiotherapy (SBRT) technique was chosen consisting of 60Gy (biologically effective dose 105Gy) in 8 fractions of 7.5Gy. Radiotherapy planning was based on MRI resulting in a

planning target volume (PTV) of 1944 cm3. Treatment toxicity was limited to a slight elevation of transaminases (grade 1 and 3). A complete resection was performed 21 weeks after radiotherapy confirmed by negative surgical margins. At last follow-up 21 months after therapy, MRI showed neither local nor distant tumor recurrence. The patient was in stable condition (ECOG 1) and without late radiation toxicity.CONCLUSIONSThis is the first documented case of liver PEComa treated by SBRT and resection. A favorable post-treatment course demonstrates that SBRT is a potential neoadjuvant treatment that is capable of reducing an inoperable rare liver tumor to a resectable lesion.

6. Phase 2 5-arm trial of ipilimumab plus lung or liver stereotactic radiation for patients with advanced malignancies

Author(s): Welsh J.W.; Tang C.; De Groot P.; Naing A.; Raju U.; Shaaban S.; Chang J.Y.; Cushman T.; Heymach J.; Dadu R.; Cabanillas M.E.; Hess K.; Subbiah V.; Fu S.; Papadimitrakopoulou V.; Gomez D.R.; Hahn S.M.; Komaki R.U.; Hong D.; Massarelli E.

Source: International Journal of Radiation Oncology Biology Physics; Dec 2017; vol. 99 (no. 5); p. 1315

Publication Date: Dec 2017

Publication Type(s): Conference Abstract

Abstract: Purpose/Objective(s): We present early toxicity and efficacy findings from a phase 2 trial that combines CTLA4 blockade (ipilimumab) with stereotactic ablative radiation therapy (SABR) targeting metastatic lung or liver lesions in patients with solid tumors. Materials/Methods: Patients with metastatic disease refractory to standard therapies with >=1 lung or liver lesion amenable to SABR and >=1 additional non-contiguous lesion were enrolled in a nonrandomized fashion. All patients were to receive ipilimumab (3 mg/kg every 3 weeks for 4 cycles) plus radiation given either concomitantly (SABR started on day 2 of cycle 1) or sequentially (SABR given 1 week after the 2nd dose of Ipilimumab). The 5 treatment groups were as follows: concomitant liver 50 Gy, concomitant lung 50 Gy, sequential liver 50 Gy, sequential lung 50 Gy, and sequential 60 Gy (lung or liver for larger lesions). 50 Gy was given in 4 fractions and 60 Gy was given in 10 fractions. Toxicity was scored per the Common Terminology Criteria for Adverse Events v4.0 and were evaluated by medical and radiation oncologists. Disease response was scored per the immune-related response criteria (irRC) by an experienced radiologist. Best responses were reported as complete response (CR), partial response (PR; size decrease >=50%), progressive disease (PD; size increase >=25%), or stable disease (SD; not meeting criteria for PR/CR or PD). The Kaplan-Meier method and log-rank tests were used to assess progression-free survival (PFS) and overall survival (OS). Results: Among 100 patients (20 in each treatment group), the most common primary histologies were adeno-(nZ55) and squamous cell (nZ13) carcinomas. No grade 4-5 toxicity was observed; 27 grade 3 toxicities were related to ipilimumab (colitis [nZ8], diarrhea [nZ7], liver enzyme elevation [nZ3], bilirubin elevation [nZ1], intestinal obstruction [nZ1], hypophysitis [nZ3], and rash [nZ4]). Two grade 3 toxicities were attributed to combined ipilimumab plus SABR: liver enzyme increase (1%) and pneumonitis (1%). The concurrent and sequential lung groups had 45% and 50% of SD, and 10% and 0% PR, respectively. The concurrent and sequential liver groups showed 35% and 30% of SD, and 5% and 0% PR, respectively. Within the sequential 60 Gy group, 60% showed a favorable response. Lesions from nonesmall cell lung cancer had the highest rate of clinical benefit (SD + PR) at 67%. There was no CR to report. Median PFS time for all patients was 5 months (95% confidence interval [CI] 2.7e7.2) and median OS time was 12 months (95% CI 9.3e14.6). At 12 months, PFS and OS were better for the sequential lung group than for the sequential liver group (PFS PZ.055, CIZ 3.7e6.4; OS PZ.059, CIZ7.9e20). However, no differences in PFS (PZ.2) or OS (PZ.3) were found between the concurrent lung and liver groups. Conclusion: These data suggest that combinations of ipilimumab and SABR

have acceptable toxicity profiles and sequential treatment may provide significant clinical benefits in term of response and survival, warranting further evaluation.

7. Optimal beam margins in linac-based VMAT stereotactic ablative body radiotherapy: a Pareto front analysis for liver metastases.

Author(s): Cilla, Savino; Ianiro, Anna; Deodato, Francesco; Macchia, Gabriella; Digesù, Cinzia; Valentini, Vincenzo; Morganti, Alessio G

Source: Medical dosimetry : official journal of the American Association of Medical Dosimetrists; Nov 2017

Publication Date: Nov 2017

Publication Type(s): Journal Article

PubMedID: 29191470

Abstract: We explored the Pareto fronts mathematical strategy to determine the optimal block margin and prescription isodose for stereotactic body radiotherapy (SBRT) treatments of liver metastases using the volumetric-modulated arc therapy (VMAT) technique. Three targets (planning target volumes [PTVs] = 20, 55, and 101 cc) were selected. A single fraction dose of 26 Gy was prescribed (prescription dose [PD]). VMAT plans were generated for 3 different beam energies. Pareto fronts based on (1) different multileaf collimator (MLC) block margin around PTV and (2) different prescription isodose lines (IDL) were produced. For each block margin, the greatest IDL fulfilling the criteria (95% of PTV reached 100%) was considered as providing the optimal clinical plan for PTV coverage. Liver Dmean, V7Gy, and V12Gy were used against the PTV coverage to generate the fronts. Gradient indexes (GI and mGI), homogeneity index (HI), and healthy liver irradiation in terms of Dmean, V7Gy, and V12Gy were calculated to compare different plans. In addition, each target was also optimized with a full-inverse planning engine to obtain a direct comparison with anatomy-based treatment planning system (TPS) results. About 900 plans were calculated to generate the fronts. GI and mGI show a U-shaped behavior as a function of beam margin with minimal values obtained with a +1 mm MLC margin. For these plans, the IDL ranges from 74% to 86%. GI and mGI show also a V-shaped behavior with respect to HI index, with minimum values at 1 mm for all metrics, independent of tumor dimensions and beam energy. Full-inversed optimized plans reported worse results with respect to Pareto plans. In conclusion, Pareto fronts provide a rigorous strategy to choose clinical optimal plans in SBRT treatments. We show that a 1-mm MLC block margin provides the best results with regard to healthy liver tissue irradiation and steepness of dose fallout.

8. Phase 1 study of pembrolizumab and stereotactic or hypofractionated radiation for metastatic non-small cell lung cancer

Author(s): Tang C.; Gomez D.R.; Chang J.Y.; Lin S.H.; Liao Z.; Komaki R.U.; Hahn S.M.; Welsh J.W.; De Groot P.; Shabaan S.; Paraskevopoulos T.; Raju U.; Papadimitrakopoulou V.; Hess K.; Simon G.R.; Glisson B.S.; Fossella F.V.; Heymach J.

Source: International Journal of Radiation Oncology Biology Physics; Oct 2017; vol. 99 (no. 2)

Publication Date: Oct 2017

Publication Type(s): Conference Abstract

Abstract: Purpose/Objective(s): Preclinical models suggest the potential for systemic disease control with PD1 inhibition and radiation. Despite promising clinical efficacy as a monotherapy in NSCLC, PD1 inhibitors have produced instances of serious immune-related pneumonitis. We describe early outcomes from a completed two-arm phase I trial combining pembrolizumab with radiation for non-

small cell lung cancer (NSCLC). Purpose/Objective(s): In NCT02444741 metastatic NSCLC were enrolled in one of two parallel arms. In the stereotactic ablative radiation (SABR) arm, patients were treated to 50 Gy in 4 fractions to a single lung or a liver lesion. In the hypofractionated radiation arm, patients were treated to 45 Gy in 15 fractions to a larger field. A simultaneous integrated boost was allowed up to 60 Gy. Pembrolizumab was given every 3 weeks and initiated the day of or day before the first dose of radiation. The trial design was a 3 + 3 phase I dose escalation testing pembrolizumab at 100 mg and then 200 mg. Both arms were independently escalated. Dose-limiting toxicities (DLTs) were grade 3+ toxicity attributable to the combination of both therapies. Progression-free survival (PFS) and overall survival (OS) were estimated by the method of Kaplan and Meier. Results: A total of 21 patients were enrolled. Among them, 2 patients did not receive treatment (1 died and 1 withdrew consent). The maximum tolerated pembrolizumab dose was 200 mg for both arms. Among the remaining 19 patients, 10 were treated with SABR (all lung lesions) and 9 with hypofractionated radiation (7 liver and 2 lung lesions). No DLTs were observed. Eight and 3 patients had grade 2 and 3 treatment-related toxicity, respectively. No grade 4 or 5 toxicities were observed. Among the 3 patients who experienced grade 3 toxicities, 1 had pneumonitis and lung infection, 1 had anemia and fatigue, and the last had a maculopapulary rash. Thirteen patients were taken off study for disease progression (n = 9), toxicity (n = 2), and withdrawal of consent (n = 2). The median follow-up time was 7.5 months, with 6-month OS 77% (95% CI: 56%-97%) and PFS 55% (95% CI: 31%-78%). Of the 19 patients who received treatment, the best recorded response was partial response in 6 patients (32%), stable disease in 7 patients (36%), and progressive disease in 6 patients (32%). Conclusion: Toxicity associated with pembrolizumab and chest radiation was acceptable. The efficacy, although preliminary, is promising and is being further assessed in the randomized phase II portion comparing radiation and pembrolizumab versus pembrolizumab.

9. Central hepatobiliary tract tolerance after stereotactic ablative radiation therapy for hepatocellular carcinoma with major portal vein tumor thrombosis: A toxicity analysis from a phase 2 study

Author(s): Kang H.C.; Kim J.H.; Kim W.C.; Kim M.S.; Kang K.M.

Source: International Journal of Radiation Oncology Biology Physics; Oct 2017; vol. 99 (no. 2)

Publication Date: Oct 2017

Publication Type(s): Conference Abstract

Abstract: Purpose/Objective(s): To identify predictors of hepatobiliary (HB) toxicity in patients who received stereotactic ablative radiotherapy (SABR) for major portal vein tumor thrombosis (MPVTT) from hepatocellular carcinoma (HCC). Purpose/Objective(s): A total of 28 patients received SABR for MPVTT in a prospective phase II trial between May 2013 and July 2015. All patients had cirrhosis with Child-Pugh score <8. The prescribed dose was 40 Gy in four fractions. Dose reduction was permitted for normal organ dose constrains. The bile duct (BD) was delineated from the common bile duct to the first bifurcation of left and right intrahepatic duct. In addition, the central hepatobiliary tract (cHBT) was defined by a 10 or 15 mm expansion of the portal vein from the splenic confluence to the first bifurcation of left and right portal veins. We analyzed the clinical and dosimetric parameters, including multiple dose-volume histogram endpoints: Dmax (the maximum point dose), Dmean (the mean dose), V40Gy (volume of cHBT that received 40 Gy), V37Gy, V34Gy. Receiver operator curves (ROC) defined optimal dosimetric thresholds for analysis. HB toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0 and we defined grade 3+ HB toxicity as a severe HB toxicity. Results: Median follow-up duration was 9.9 months after SABR. Eight out of 28 patients (28.6%) experienced severe HB toxicity. Among clinical and dosimetric parameters, V40Gy of cHBT with 10 mm expansion were highly associated with severe HB toxicity: V40Gy>40 cm3 (relative risk [RR] = 3.2, P < 0.011). However, clinical or other dosimetric factors, Dmax or Dmean of BD and cHBT, did not have predictive value. The risk of severe

HB toxicity for V40Gy<= 20 cm3, > 20 cm3, > 30 cm3, and > 40 cm3 are 8.3% (n = 1/12), 41.2% (n = 7/17), 46.2% (n = 6/13), and 54.5% (n = 6/11), respectively. Conclusion: SABR to the central liver lesions should be used with caution due to the risk of HB toxicity. Radiation doses to cHBT are associated with development of severe HB toxicity. We suggest that V40Gy<20 cm3 as a potential dose constraint for cHBT when delivered in four fractions.

Radium 223 - Prostate and breast metastases

1. Bone-targeted therapies to reduce skeletal morbidity in prostate cancer.

Author(s): Dorff, Tanya B; Agarwal, Neeraj

Source: Asian journal of andrology; 2018; vol. 20 (no. 3); p. 215-220

Publication Date: 2018

Publication Type(s): Journal Article Review

PubMedID: 29553053

Available at Asian Journal of Andrology - from Europe PubMed Central - Open Access

Available at Asian Journal of Andrology - from EBSCO (MEDLINE Complete)

Available at Asian Journal of Andrology - from ajandrology.com

Abstract: Bone metastases are the main driver of morbidity and mortality in advanced prostate cancer. Targeting the bone microenvironment, a key player in the pathogenesis of bone metastasis, has become one of the mainstays of therapy in men with advanced prostate cancer. This review will evaluate the data supporting the use of bone-targeted therapy, including (1) bisphosphonates such as zoledronic acid, which directly target osteoclasts, (2) denosumab, a receptor activator of nuclear factor-kappa B (RANK) ligand inhibitor, which targets a key component of bone stromal interaction, and (3) radium-223, an alpha-emitting calcium mimetic, which hones to the metabolically active areas of osteoblastic metastasis and induces double-strand breaks in the DNA. Denosumab has shown enhanced delay in skeletal-related events compared to zoledronic acid in patients with metastatic castration-resistant prostate cancer (mCRPC). Data are mixed with regard to pain control as a primary measure of efficacy. New data call into question dosing frequency, with quarterly dosing strategy potentially achieving similar effect compared to monthly dosing for zoledronic acid. In the case of radium-223, there are data for both pain palliation and improved overall survival in mCRPC. Further studies are needed to optimize timing and combination strategies for bone-targeted therapies. Ongoing studies will explore the impact of combining bone-targeted therapy with investigational therapeutic agents such as immunotherapy, for advanced prostate cancer. Future studies should strive to develop biomarkers of response, in order to improve efficacy and cost-effectiveness of these agents.

2. Ra223 in Bone Metastases with Osteolytic Activity.

Author(s): Costa, Renato Patrizio; Cardile, Davide; Murabito, Alessandra; Tripoli, Vincenzo; Verderame, Francesco

Source: World journal of nuclear medicine; 2018; vol. 17 (no. 2); p. 116-119

Publication Date: 2018

Publication Type(s): Journal Article

PubMedID: 29719487

Available at World Journal of Nuclear Medicine - from Europe PubMed Central - Open Access

Available at World Journal of Nuclear Medicine - from PubMed Central

Abstract: Radium 223 dichloride (Ra223) is the only targeted alpha therapy able to extend survival in patients with bone metastases from prostate cancer. Mechanism of action and data currently available focused mainly on osteoblastic metastases from prostate cancer. In our institution, a patient with breast cancer affected by osteolytic metastases was treated with off-label use of Ra223. The evaluation of the deposit areas of Ra223 showed a perfect overlap with the regions of osteolysis previously detected by scintigraphy, indicating a possible therapeutic effect. This case report is the first document attesting Ra223 deposit in osteolytic metastases opening new opportunity of therapeutic development for this radiopharmaceutical.

3. The Clinical Efficacy of Radium-223 for Bone Metastasis in Patients with Castration-Resistant Prostate Cancer: An Italian Clinical Experience.

Author(s): De Luca, Rossella; Costa, Renato Patrizio; Tripoli, Vincenzo; Murabito, Alessandra; Cicero, Giuseppe

Source: Oncology; 2018; vol. 94 (no. 3); p. 161-166

Publication Date: 2018

Publication Type(s): Journal Article

PubMedID: 29241166

Abstract:BACKGROUND/AIMProstate cancer frequently causes bone metastases and skeletal events that impair quality of life (QoL) and survival. The alpha emitter radium-223 is a new drug that improves treatment in men with castration-resistant prostate cancer (CRPC) and bone metastases. Our aim was to evaluate the effectiveness of radium-223.SUBJECTS AND METHODSIn this retrospective study we enrolled 48 subjects. Pain reduction, alkaline phosphatase (ALP), time to first symptomatic skeletal event, and QoL were the variables we evaluated.RESULTSRadium-223 was well tolerated, with a manageable toxicity profile and a modest objective response rate. A considerable difference in serum ALP levels before and after treatment was observed, with a significant correlation between pain relief and QoL, which showed a value of R2 to 0.44 with a slope of 1.50 ($p = 0.0021$).CONCLUSIONSRadium-223 showed a clinical benefit, with a reduction in pain symptoms in 58% of patients. Radium-223 was shown to be an effective and well-tolerated therapeutic option in patients with metastatic CRPC progressing after docetaxel plus prednisone treatment.

4. Utility of F-18 FDG PET/CT for Detection of Bone Marrow Metastases in Prostate Cancer Patients Treated with Radium-223.

Author(s): Maruyama, Kaoru; Utsunomia, Keita; Nakamoto, Takahiro; Kawakita, Shigenari; Murota, Takashi; Tanigawa, Noboru

Source: Asia Oceania journal of nuclear medicine & biology; 2018; vol. 6 (no. 1); p. 61-67

Publication Date: 2018

Publication Type(s): Journal Article

PubMedID: 29333469

Available at Asia Oceania journal of nuclear medicine & biology - from Europe PubMed Central - Open Access

Available at Asia Oceania journal of nuclear medicine & biology - from mums.ac.ir

Abstract:A 76-year-old man with symptomatic bone metastases from castration-resistant prostate cancer underwent Radium-223-dichloride (Ra-223) therapy. Before Ra-223 therapy, he had normal peripheral blood cell counts. Ra-223 therapy relieved his shoulder and low back pain. The elevation of the serum prostate-specific antigen (PSA), doubling every month during Ra-223 therapy, suggested a PSA flare or relapse. Some lesions showed decrease and some lesions showed increase on Tc-99m hydroxymethylene diphosphonate bone scintigraphy at two weeks after the third injection of Ra-223 therapy. Ra-223 therapy was discontinued due to thrombocytopenia that was getting worse rapidly. After treatment discontinuation, namely four weeks after the third injection of Ra-223, F-18 fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/CT and a biopsy were performed to evaluate for metastases, and bone marrow metastases were found. Ra-223 was effective for osteoblastic lesions, but not for bone marrow metastases. FDG PET/CT, but not a Tc-99m based bone scan, detected diffuse bone marrow involvement by cancer. This case report is the first to clarify the utility of FDG PET for the detection of bone marrow metastases confirmed by pathological examination in Ra-223 therapy for progressive castration-resistant prostate cancer.

5. Systematic Review and Network Meta-Analysis of Treatments for Chemotherapy-Naive Patients with Asymptomatic/Mildly Symptomatic Metastatic Castration-Resistant Prostate Cancer

Author(s): McCool R.; Glanville J.; Arber M.; Fleetwood K.; Goodall H.; Naidoo S.

Source: Value in Health; 2018

Publication Date: 2018

Publication Type(s): Article In Press

Abstract: Objectives: To estimate the relative effectiveness of enzalutamide in chemotherapy-naive metastatic castration-resistant prostate cancer by conducting a systematic literature review and a network meta-analysis (NMA). Methods: A systematic literature review identified randomized controlled trials comparing enzalutamide, abiraterone/prednisone, radium-223, sipuleucel-T, or docetaxel with each other or placebo in chemotherapy-naive or mixed populations (with and without prior chemotherapy) with asymptomatic/mildly symptomatic metastatic castration-resistant prostate cancer. Feasibility assessment evaluated the trials' suitability for NMA inclusion. The main outcomes were hazard ratios (HRs) for overall survival (OS) and radiographic progression-free survival (rPFS). Results: Searches of relevant bibliographic databases, trial registers, Web sites, and conference abstracts conducted in October 2014 identified 25,712 records. Ten randomized controlled trials were eligible for the NMA. Enzalutamide was superior to placebo for OS and rPFS (fixed-effects model). NMA results (fixed-effects model) showed no evidence of a difference between enzalutamide and abiraterone/prednisone (HR 0.95 [95% CrI 0.77-1.16]), sipuleucel-T (HR 1.07 [95% CrI 0.84-1.37]), or radium-223 (HR 1.10 [95% CrI 0.87-1.37]) for OS. HRs were similar for the random-effects model. Nevertheless, results (fixed-effects model) suggested that enzalutamide was superior to abiraterone/prednisone (HR 0.59 [95% CrI 0.48-0.72]) and sipuleucel-T (HR 0.32 [95% CrI 0.25-0.42]) for rPFS. Results also suggested superiority of enzalutamide versus placebo, abiraterone/prednisone, or sipuleucel-T for time to chemotherapy. Conclusions: For rPFS, the NMA suggests that enzalutamide is superior to abiraterone/prednisone and sipuleucel-T. There is no evidence of a statistically significant difference in OS between enzalutamide and abiraterone/prednisone, sipuleucel-T, or radium-223. Given the limitations in network construction and underlying assumptions made to complete these analyses, results should be interpreted with caution.

6. First interim results of PARABO - A non-interventional Study evaluating patients with mCRPC with bone metastases treated with Radium-223 (Xofigo) in a real life German practice setting

Author(s): Palmedo P.; Eschmann E.; Werner W.; Selinski S.; Mollers M.; Pinkert J.; Van Cruchten C.; Neusser N.; Poppel P.

Source: NuklearMedizin; 2018; vol. 57 (no. 2)

Publication Date: 2018

Publication Type(s): Conference Abstract

Abstract: Ziel/Aim: Ra-223 is the first in class targeted alpha therapy proven to extend survival with good safety in metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 ALSYMPCA trial. PARABO will evaluate Ra-223 safety and efficacy parameters (pain response, QoL and OS) in routine clinical practice in Germany. Methodik/Methods: This prospective, single-arm, observational study will enroll 350 pts with mCRPC with bone metastases (mets) for whom Ra-223 therapy was initiated. Follow-up will continue up to 2 years after last Ra-223 dose. This interim analysis was done after 188 patients had finished their therapy with Ra-223. We conducted a descriptive analysis of baseline characteristics, safety and efficacy of patients based on number of Ra-223 injections received using data from this first interim analysis. Ergebnisse/Results: Patients were enrolled from March 2015 to May 2017. Data are available from 63 pts who received 1- 4 injections Ra-223 vs. 125 (66.5%) patients who received 5-6 injections. Overall treatment-emergent AEs occurred in 93 pts (49.5%). Blood and lymphatic system disorders grade >=3 occurred in 11 pts (17.5%) and 5 (4.0%) in patients who received 1-4 and 5-6 injections, respectively. Schlussfolgerungen/Conclusions: In a real life clinical practice setting Ra-223 was associated with no short-term safety concerns and appeared to be used in pts with less advanced mCRPC as observed in ALSYMPCA. The majority of pts on Ra-223 received 5-6 doses. Patients receiving Ra-223 in an early stage of disease, as suggested by lower ECOG, less opioid use and lower burden of disease, have a greater chance to complete Ra-223 therapy. Ra-223 was often used with abiraterone or enzalutamide, but rarely with chemotherapy.

7. Uptake of Radium-223 Dichloride and Early [18F]NaF PET Response Are Driven by Baseline [18F]NaF Parameters: a Pilot Study in Castration-Resistant Prostate Cancer Patients.

Author(s): Letellier, Arthur; Johnson, Alison C; Kit, Nicolas How; Savigny, Jean-François; Batalla, Alain; Parienti, Jean-Jacques; Aide, Nicolas

Source: Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging; Jun 2018; vol. 20 (no. 3); p. 482-491

Publication Date: Jun 2018

Publication Type(s): Journal Article

PubMedID: 29027074

Abstract:PURPOSEThe purpose of this study is to identify predictive factors on baseline [18F]NaF positron emission tomography (PET)/computed tomography (CT) of early response to radium-223 dichloride after 3 cycles of treatment in metastatic castration-resistant prostate cancer patients.PROCEDURESAnalysis of 152 metastases was performed in six consecutive patients who underwent [18F]NaF PET/CT at baseline and for early monitoring after 3 cycles of radium-223 dichloride. All metastases depicted on whole-body [18F]NaF PET/CT were contoured and CT (density in Hounsfield units, sclerotic, mixed, or lytic appearance) as well as [18F]NaF [maximum standardized uptake value (SUVmax), SUVmean, and lesion volume (V18F-NaF)] patterns were recorded. Tumor response was defined as percentage change in SUVmax and SUVmean between baseline and post-treatment PET. Bone lesions were defined as stable, responsive, or progressive, according to thresholds derived from a recent multicentre test-retest study in [18F]NaF PET/CT. Total [18F]NaF uptake in metastases, defined as MATV × SUVmean, was correlated to uptake of radium-223 on biodistribution scintigraphy performed 7 days after the first cycle of treatment.RESULTSAmong metastases, 116 involved the axial skeleton and 36 the appendicular

skeleton. Lesions were sclerotic in 126 cases and mixed in 26 cases. No lytic lesion was depicted. ROC analysis showed that SUVmax and SUVmean were better predictors of lesion response than V18F-NaF and density on CT (P < 0.0001 and P = 0.001, respectively). SUVmax and SUVmean were predictors of individual tumor response in separate multivariate models (P = 0.01 and P = 0.02, respectively). CT pattern (mixed versus sclerotic) and lesion density were independent predictors only when assessing response with delta SUVmax (P = 0.002 and 0.007, respectively). A good correlation between total [18F]NaF uptake within metastases and their relative radium-223 uptake assessed by two observers 7 days after treatment (r = 0.72 and 0.77, P < 0.0001) was found.CONCLUSIONSSUVmax and SUVmean on baseline [18F]NaF PET/CT are independent predictors of bone lesions' response to 3 cycles of radium-223 dichloride, supporting the use of NaF to select patients more likely to respond to treatment.

8. Selection and monitoring of patients with metastatic castration-resistant prostate cancer for treatment with radium-223.

Author(s): Rodriguez-Vida, A; Torregrosa, M D; Pinto, Á; Climent, M Á; Olmos, D; Carles, J

Source: Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico; Jun 2018; vol. 20 (no. 6); p. 679-686

Publication Date: Jun 2018

Publication Type(s): Journal Article Review

PubMedID: 29098556

Abstract: Despite the improvement provided by androgenic suppression in the treatment of prostate cancer, most of tumors develop resistance to castration. However, new therapies have demonstrated an increase in patient survival such as radium-223 (Ra-223), an alpha emitter and calcium mimetic with the capability of targeting osteoblastic metastatic lesions. According to results of the ALSYMPCA phase III trial, Ra-223 has demonstrated its activity by improving symptoms and survival of patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases, and no known visceral metastatic disease, without interfering with subsequent treatments. This review examines the key evidence to establish the best patient selection criteria to use Ra-223, how to assess the response to treatment, treatment-related toxicity, and follow-up, but also current research regarding imaging techniques and biomarkers to assess the efficacy of Ra-223. Finally, we briefly describe the clinical trials that are currently ongoing with Ra-223.

9. EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer.

Author(s): Poeppel, Thorsten D; Handkiewicz-Junak, Daria; Andreeff, Michael; Becherer, Alexander; Bockisch, Andreas; Fricke, Eva; Geworski, Lilli; Heinzel, Alexander; Krause, Bernd J; Krause, Thomas; Mitterhauser, Markus; Sonnenschein, Wilfried; Bodei, Lisa; Delgado-Bolton, Roberto C; Gabriel, Michael

Source: European journal of nuclear medicine and molecular imaging; May 2018; vol. 45 (no. 5); p. 824-845

Publication Date: May 2018

Publication Type(s): Journal Article

PubMedID: 29234845

Abstract: Radium Ra-223 dichloride (radium-223, Xofigo®) is a targeted alpha therapy approved for the treatment of castration-resistant prostate cancer (CRPC) with symptomatic bone metastases and no known visceral metastatic disease. Radium-223 is the first targeted alpha therapy in this

indication providing a new treatment option, with evidence of a significant survival benefit, both in overall survival and in the time to the first symptomatic skeletal-related event. The skeleton is the most common metastatic site in patients with advanced prostate cancer. Bone metastases are a clinically significant cause of morbidity and mortality, often resulting in bone pain, pathologic fracture, or spinal cord compression necessitating treatment. Radium-223 is selectively accumulated in the bone, specifically in areas of high bone turnover, by forming complexes with the mineral hydroxyapatite (the inorganic matrix of the bone). The alpha radiation generated during the radioactive decay of radium-223 produces a palliative anti-tumour effect on the bone metastases. The purpose of this guideline is to assist nuclear medicine specialists in evaluating patients who might be candidates for treatment using radium-223, planning and performing this treatment, understanding and evaluating its consequences, and improving patient management during therapy and follow-up.

10. Radium-223 in the therapeutic sequence of metastatic castration-resistant prostate cancer.

Author(s): Unda-Urzaiz, M; Sousa-Campo, R; Rodríguez-Antolín, A; Silva-Marins, C; Juárez-Soto, A; Miñana-López, B; Figueiredo-de Castro, A; Cozar-Olmos, J M

Source: Actas urologicas espanolas; May 2018; vol. 42 (no. 4); p. 227-237

Publication Date: May 2018

Publication Type(s): Journal Article

PubMedID: 28711312

Abstract:CONTEXTRadium-223 is an □ -particle transmitter with specific action on bone metastases. The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study showed that radium-223 extended overall survival and delayed the onset of bone events in patients with symptomatic castration-resistant prostate cancer with bone metastases (mCRPC) and without visceral metastases, with a good safety profile.OBJECTIVETo review the new scientific evidence on radium-223 based on prespecified and post-hoc analyses of the ALSYMPCA study and on early-access programs after the publication of the ALSYMPCA study, thereby providing new data on the management of patients with mCRPC.ACQUISITION OF EVIDENCEWe searched for evidence on PubMed and in the abstracts of international urology and oncology congresses, as well as ongoing clinical trials (ClinicalTrials.gov).SYNTHESIS OF THE EVIDENCEThe results of the reviewed studies offer promising results that will broaden the therapeutic benefits of radium-223 to patients with mild symptoms and those with no symptoms. The results also provide preliminary evidence on the benefit of radium-223 treatment after the failure of docetaxel, enzalutamide or abiraterone or the combination of radium-223 with these agents or other therapeutic agents such as bone-targeted agents and immunotherapy.CONCLUSIONRadium-223 can be a treatment option for patients with mild symptoms and can provide a therapeutic benefit after failure of currently available treatments or in combination with these treatments. This evidence should be corroborated in clinical trials before being added to clinical practice.

11. Is There a Flare Phenomenon on Bone Scintigraphy in Men With Advanced Prostate Cancer Treated With Radium-223?

Author(s): Isensee, Gesa; Péporté, Anne; Müller, Joachim; Schmid, Sabine; Gillessen, Silke; Omlin, Aurelius

Source: Clinical genitourinary cancer; Apr 2018

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29778323

Abstract:INTRODUCTIONRadium-223 is an approved survival-prolonging treatment option in men with castration-resistant prostate cancer (mCRPC) and bone metastases. In the registration trial (ALSYMPCA), no regular imaging was mandated. We aimed to analyze men with metastatic mCRPC treated with radium-223 who had bone scintigraphy for staging and treatment monitoring.PATIENTS AND METHODSRetrospective chart review was performed of mCRPC patients who received 6 cycles of radium-223 and who underwent bone scintigraphy before start of radium-223 and after 3 and 6 cycles of treatment.RESULTSNineteen patients with a median age of 74 years met the selection criteria and were included in the analysis. On bone scintigraphy, 4 of 19 patients showed a total of ≥ 2 new lesions after 3 cycles of radium-223 therapy, but 3 of 4 patients did not have ≥ 2 new lesions after 6 cycles, meeting the criteria for bone scintigraphy flare. Of these 4 patients, 2 received radium-223 before docetaxel therapy, and all 4 had concomitant treatment with denosumab. In the entire cohort, 3 of 19 patients showed soft tissue progression on computed tomography after 3 cycles of radium-223.CONCLUSIONBone scintigraphy flare in patients undergoing therapy with radium-223 was observed. Bone scintigraphy data acquired during treatment with radium-223 should be interpreted with caution, and treatment should not be changed according to increase in number of lesions on bone scintigraphy alone after 3 cycles of radium-223.

12. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology.

Author(s): Nuhn, Philipp; De Bono, Johann S; Fizazi, Karim; Freedland, Stephen J; Grilli, Maurizio; Kantoff, Philip W; Sonpavde, Guru; Sternberg, Cora N; Yegnasubramanian, Srinivasan; Antonarakis, Emmanuel S

Source: European urology; Apr 2018

Publication Date: Apr 2018

Publication Type(s): Journal Article Review

PubMedID: 29673712

Abstract:CONTEXTIntroduction of novel agents for the management of advanced prostate cancer provides a range of treatment options with notable benefits for men with metastatic castration-resistant prostate cancer (mCRPC). At the same time, understanding of optimal patient selection, effective sequential use, and development of resistance patterns remains incomplete.OBJECTIVETo review current systemic therapies and recent advances in drug development for mCRPC and strategies to aid in patient selection and optimal sequencing.EVIDENCE ACQUISITIONA literature review of PubMed/Medline, Cochrane Library, Current Contents Medicine, Web of Science, Clinical Trial.Gov, WHO-ICTRP (January 2004-November 2017), and the proceedings of major international meetings (2015/2016/2017) was performed in November 2017.EVIDENCE SYNTHESISIn the last few years, several new options for treatment of mCRPC have shown a survival benefit in phase III trials besides docetaxel:abiraterone, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T. Radium-223 and denosumab have increased options in management of bone metastases. Currently, novel agents such as next-generation androgen receptor (AR) axis-targeting treatments, immunotherapeutics, or therapies targeting other oncogenic and genomic pathways, particularly poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors and PD-1 inhibitors, are under clinical investigation. With increasing treatment options for mCRPC, information on how to personalize management and how to select and sequence existing therapies is beginning to emerge, as are predictive biomarkers (homologous repair mutations, mismatch repair mutations, AR splice variant 7). Finally, early use of active agents in the castration-sensitive state will likely also change the clinical management of the disease when it becomes castrate resistant.CONCLUSIONSThe emergence of new drugs for mCRPC has improved treatment options dramatically. Currently,

systemic treatment options for mCRPC include hormonal therapy, chemotherapy, immunotherapy, and radionuclide therapy as well as bone-modifying agents and palliative or supportive measures. Further, new genetically targeted agents (PARP inhibitors and PD-1 inhibitors) are on the horizon for certain subsets of biomarker-selected patients. The best strategies for patient selection and optimal sequential use to achieve the longest cumulative survival improvement and to prevent early resistance remain unclear.PATIENT SUMMARYThe current literature and proceedings from relevant congresses related to available systemic agents for the treatment of metastatic castration-resistant prostate cancer, including novel genetically targeted therapies, including poly(adenosine diphosphate-ribose) polymerase inhibitors and PD-1 inhibitors, were reviewed. Current therapies and ongoing developments are discussed.

13. Radium-223 in the treatment of bone metastasis in patients with castration-resistant prostate cancer. Review and procedure.

Author(s): Orcajo-Rincon, J; Caresia-Aróztegui, A P; Del Puig Cózar-Santiago, M; García-Garzón, J R; de Arcocha-Torres, M; Delgado-Bolton, R C; García-Velloso, M J; Alvarez-Ruiz, S; García-Vicente, A M

Source: Revista espanola de medicina nuclear e imagen molecular; Apr 2018

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29661653

Abstract: Bone metastatic disease is the main cause of morbidity / mortality in patients with prostate cancer, presenting frequently as bone pain, pathological fractures or spinal cord compression, which requires early and timely therapy. Although, for the moment, the therapeutic window for its use has not been definitively established, radium-223 (223Ra), an alpha particle emitter, has proved to be an effective therapeutic tool, pre or post-chemotherapy, in patients with castration-resistant prostate cancer with symptomatic bone metastases and absence of visceral metastases, significantly modifying the prognosis of the disease. It is therefore imperative to define the ideal scenarios and the correct protocol for the use of this therapy and thus offer the greatest possible clinical benefit to the patient.

14. Treatment of Metastatic, Castration-Resistant, Docetaxel-Resistant Prostate Cancer: A Systematic Review of Literature With a Network Meta-Analysis of Randomized Clinical Trials.

Author(s): Tassinari, Davide; Cherubini, Chiara; Roudnas, Britt; Tamburini, Emiliano; Drudi, Fabrizio; Bianchi, Emanuela; Fantini, Manuela; Montanari, Francesco; Sartori, Sergio

Source: Reviews on recent clinical trials; Apr 2018

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29623850

Abstract:INTRODUCTIONTo compare the efficacy of abiraterone acetate, enzalutamide, cabazitaxel and Radium-223 in the treatment of castration-resistant, docetaxel-resistant metastatic prostate cancer.METHODSAn indirect comparison of overall survival (OS) and time to PSA progression among abiraterone acetate, enzalutamide, cabazitaxel and Radium-223 was performed with a network meta-analysis. OS in the entire population of patients was the primary end point. OS in ECOG 0-1/2, BPI-SF≤4/>4, pretreated with 1 or 2 courses of chemotherapy, age≤65/>65 patients, patients with only bone metastases or bone and visceral metastases, and time to PSA progression were the secondary end points. An indirect comparison of the Hazard Ratio and the 95% Confidence Interval was performed, assuming an alpha error of 5% as index of statistical significance. The among-the-

trial heterogeneity was assessed using a qualitative methodological and clinical analysis.RESULTSFour trials were selected. In three trials the comparator was placebo, in one trial it was mitoxantrone, the effect of which in improving survival was considered negligible. No significant difference in OS among abiraterone acetate, enzalutamide, cabazitaxel and radium 223 was observed in neither the entire population nor all the subgroups of patients. Enzalutamide resulted significantly better than abiraterone acetate, cabazitaxel or radium-223 in time to PSA progression.CONCLUSIONSince no significant difference in efficacy seems to exist between the four therapeutic options in the treatment of castration-resistant, docetaxel-resistant, metastatic prostate cancer, the safety of the treatment, patient's compliance and costs should represent the criteria to guide clinicians' choice in clinical practice.

15. 223Ra-chloride therapy in men with hormone-refractory prostate cancer and skeletal metastases: Real-world experience.

Author(s): Boni, Giuseppe; Mazzarri, Sara; Cianci, Claudia; Galli, Luca; Farnesi, Azzurra; Borsatti, Eugenio; Bortolus, Roberto; Fratino, Lucia; Gobitti, Carlo; Lamaj, Elda; Ghedini, Pietro; Rizzini, Elisa Lodi; Massari, Francesco; Dionisi, Valeria; Fanti, Stefano; Volterrani, Duccio; Monari, Fabio

Source: Tumori; Apr 2018 ; p. 300891618765571

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29714668

Abstract:BACKGROUNDRadium-223 (223Ra) chloride, an alpha emitter, has been shown to improve overall survival (OS) and pain control, and to delay skeletal-related events, in patients with castration-resistant prostate cancer (CRPC) and bone metastases. Our retrospective observational study presents the first Italian experience on the efficacy and safety of 223Ra therapy in routine clinical practice.METHODSA total of 83 patients with metastatic CRPC were treated with 223Ra at 3 Italian centers between August 2013 and August 2016. 223Ra-chloride (55 kBq/kg) was administered every 4 weeks for a total of 6 cycles. Primary endpoints were OS and progression-free survival (PFS). Secondary endpoints included toxicity, pain evaluation using numeric rating scale (NRS), symptomatic skeletal-related events and biomarkers response.RESULTSPatients had a median age of 75 (range 53-89) years. The majority of men showed a Gleason score of 7, 8, or 9. Forty-one patients completed 6 treatment cycles; 33 stopped treatment before completing 6 cycles. Nine were still receiving therapy at the time of data collection. At the end of therapy, NRS pain scores significantly improved ($p < .000001$). OS was a mean of 10.1 months, while median OS had not been attained. According to Kaplan-Meier estimation, OS and PFS were 17.5 and 7.7 months, respectively. There was a significant correlation between OS and PFS with the number of 223Ra cycles; patients receiving all 6 cycles experienced the major benefit from the therapy. 223Ra was well-tolerated.CONCLUSIONS223Ra alpha therapy is an important therapeutic option for men with CRPC and symptomatic skeletal metastases.

16. EMA guidance on radium-223 dichloride in prostate cancer.

Author(s): Gourd, Elizabeth

Source: The Lancet. Oncology; Apr 2018; vol. 19 (no. 4); p. e190

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29551361

17. Alpha-Emitters and Targeted Alpha Therapy in Oncology: from Basic Science to Clinical Investigations.

Author(s): Makvandi, Mehran; Dupis, Edouard; Engle, Jonathan W; Nortier, F Meiring; Fassbender, Michael E; Simon, Sam; Birnbaum, Eva R; Atcher, Robert W; John, Kevin D; Rixe, Olivier; Norenberg, Jeffrey P

Source: Targeted oncology; Apr 2018; vol. 13 (no. 2); p. 189-203

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29423595

Abstract: Alpha-emitters are radionuclides that decay through the emission of high linear energy transfer α-particles and possess favorable pharmacologic profiles for cancer treatment. When coupled with monoclonal antibodies, peptides, small molecules, or nanoparticles, the excellent cytotoxic capability of α-particle emissions has generated a strong interest in exploring targeted α-therapy in the pre-clinical setting and more recently in clinical trials in oncology. Multiple obstacles have been overcome by researchers and clinicians to accelerate the development of targeted α-therapies, especially with the recent improvement in isotope production and purification, but also with the development of innovative strategies for optimized targeting. Numerous studies have demonstrated the in vitro and in vivo efficacy of the targeted α-therapy. Radium-223 (223Ra) dichloride (Xofigo®) is the first α-emitter to have received FDA approval for the treatment of prostate cancer with metastatic bone lesions. There is a significant increase in the number of clinical trials in oncology using several radionuclides such as Actinium-225 (225Ac), Bismuth-213 (213Bi), Lead-212 (212Pb), Astatine (211At) or Radium-223 (223Ra) assessing their safety and preliminary activity. This review will cover their therapeutic application as well as summarize the investigations that provide the foundation for further clinical development.

18. Current approaches to incorporation of radium-223 in clinical practice.

Author(s): Parker, Chris; Heidenreich, Axel; Nilsson, Sten; Shore, Neal

Source: Prostate cancer and prostatic diseases; Apr 2018; vol. 21 (no. 1); p. 37-47

Publication Date: Apr 2018

Publication Type(s): Journal Article Review

PubMedID: 29298991

Abstract:BACKGROUNDTreatment options for metastatic castration-resistant prostate cancer (mCRPC) have expanded in recent years and include cytotoxic agents (e.g., docetaxel and cabazitaxel), immunotherapy (e.g., sipuleucel-T), oral hormonal therapies targeting the androgen receptor axis (e.g., enzalutamide and abiraterone), and targeted alpha therapy (e.g., radium-223 dichloride (radium-223)). Although treatment guidelines have been updated to reflect the availability of new agents, it is not easy to apply them in daily clinical practice because recommendations vary depending on patient comorbidities and disease characteristics. Furthermore, therapeutic accessibility, clinical judgment, and experience affect the selection of treatment options.METHODSIn this review, we provide practical guidance for the integration of radium-223 into the management of patients with mCRPC based on our collective clinical experience, as well as the available clinical trial data.RESULTSRadium-223 is a targeted alpha therapy; as a bone-seeking calcium mimetic, it accumulates in hydroxyapatite areas surrounding tumor lesions and selectively binds to the areas of increased bone turnover. Radium-223 prolongs overall survival and delays time to the first symptomatic skeletal events in men with mCRPC, and is indicated for the treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastases. We review its clinical efficacy and safety, practical guidance on identifying the

appropriate patient, and recommendations for how best to educate and inform prospective patients regarding their treatment decision making. In addition, we review recent evidence for sequential and combination therapies with radium-223, provide our experiences with these treatment approaches, and discuss their implications for the future treatment of patients with mCRPC.CONCLUSIONSBased on our clinical experience, radium-223 should be considered relatively early in the treatment course in patients with mCRPC with bone metastases. Coordination of care among multidisciplinary team members, patients, and caregivers is essential for optimizing safe and effective treatment with all CRPC therapies.

19. Optical emission of 223 Radium: in vitro and in vivo preclinical applications.

Author(s): Boschi, Federico; De Sanctis, Francesco; Spinelli, Antonello E

Source: Journal of biophotonics; Apr 2018; vol. 11 (no. 4); p. e201700209

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29055100

Abstract:223 Radium (223 Ra) is widely used in nuclear medicine to treat patients with osseous metastatic prostate cancer. In clinical practice 223 Ra cannot be imaged directly; however, gamma photons produced by its short-lived daughter nuclides can be captured by conventional gamma cameras. In this work, we show that 223 Ra and its short-lived daughter nuclides can be detected with optical imaging techniques. The light emission of 223 Ra was investigated in vitro using different setups in order to clarify the mechanism of light production. The results demonstrate that the luminescence of the 223 Ra chloride solution, usually employed in clinical treatments, is compatible with Cerenkov luminescence having an emission spectrum that is almost indistinguishable from CR one. This study proves that luminescence imaging can be successfully employed to detect 223 Ra in vivo in mice by imaging whole body 223 Ra biodistribution and more precisely its uptake in bones.

20. An Observational Study of Concomitant Use of Emerging Therapies and Denosumab or Zoledronic Acid in Prostate Cancer.

Author(s): Liede, Alexander; Wade, Sally; Lethen, Jan; Hernandez, Rohini K; Warner, Douglas; Abernethy, Amy P; Finelli, Antonio

Source: Clinical therapeutics; Apr 2018; vol. 40 (no. 4); p. 536

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29395290

Abstract:PURPOSEThis observational study of oncologic clinical practices was designed to describe real-world patterns of use of emerging therapies (abiraterone acetate, cabazitaxel, enzalutamide, radium-223, sipuleucel-T) in patients with castration-resistant prostate cancer and to characterize their concomitant use with denosumab or zoledronic acid.METHODSA retrospective cohort study was conducted using a database of electronic health records from oncology practices across the United States. Eligible patients had a diagnosis of prostate cancer (International Classification of Diseases, Ninth Revision [ICD-9] code 185/International Classification of Diseases, Tenth Revision [ICD-10] code C61) before or concurrent with a visit between January 1, 2013, and December 31, 2015; follow-up was performed through June 30, 2016. From this population, we identified those who received an emerging therapy and a subset who also received denosumab or zoledronic acid.FINDINGSA total of 71,606 men met the eligibility criteria, and 5131 (7%) received emerging

therapy. In the emerging therapy cohort (at the time of the first use), median age was 75 years, median prostate-specific antigen value was 22.7 ng/mL, 56% had bone metastases, and 80% were docetaxel naive. Abiraterone and enzalutamide were the most commonly used first emerging therapies (52% and 31%, respectively), followed by sipuleucel-T (9%), cabazitaxel (5%), and radium-223 (1.5%). Of the emerging therapy cohort, 3121 patients (61%) received concomitant denosumab (70%) or zoledronic acid (35%); 5% received both.IMPLICATIONSAmong patients with prostate cancer treated in the United States, most of those treated with an emerging therapy between 2013 and 2015 also received denosumab or zoledronic acid, suggesting that the concomitant use of these therapy types is currently a common practice. Use of denosumab or zoledronic acid was higher in patients with verified bone metastases.

21. eRADicAte: A Prospective Evaluation Combining Radium-223 Dichloride and Abiraterone Acetate Plus Prednisone in Patients With Castration-Resistant Prostate Cancer.

Author(s): Shore, Neal D; Tutrone, Ronald F; Mariados, Neil F; Nordquist, Luke T; Mehlhaff, Bryan A; Steere, Karyn J; Harrelson, Stacey S

Source: Clinical genitourinary cancer; Apr 2018; vol. 16 (no. 2); p. 149-154

Publication Date: Apr 2018

Publication Type(s): Journal Article

PubMedID: 29196208

Abstract:BACKGROUNDMultiple castration-resistant prostate cancer (CRPC) therapies are approved by the United States Food and Drug Administration. Radium-223 dichloride (Ra-223) with abiraterone acetate plus prednisone have different mechanisms of action and distinct off-target side-effect profiles. We prospectively investigated their combined safety, tolerability, and patient-reported outcome measures.PATIENTS AND METHODSeRADicAte, an investigator-initiated, phase II trial, studied 31 patients with metastatic CRPC, from 5 United States uro-oncology research sites. Patients completed 6 cycles of Ra-223 with concurrent abiraterone therapy. Quality of life and pain were assessed using the Functional Assessment of Cancer Therapy-Prostate and the Brief Pain Inventory-Short Form questionnaires and their subscales; we reported the number of subjects meeting standardized criteria for clinically meaningful improvements on each scale. Safety assessment included Eastern Cooperative Oncology Group performance status, laboratory changes, opioid use, radiographic responses, and adverse events (AEs).RESULTSTwenty of 31 (65%) experienced positive clinically meaningful improvement changes on the Functional Assessment of Cancer Therapy-Prostate, and 25 (81%) of 31 on the Prostate Cancer Subscale. Eighteen (58%) of 31 demonstrated reduced pain intensity and 12 (39%) of 31 demonstrated reduction of pain interference in their lives. At baseline, subjects averaged 11.6 ± 2.8 bone lesions; at the end of treatment, subjects averaged 5.6 ± 2.4 bone lesions (P = .0002). The most frequent AEs were diarrhea (17%), nausea (17%), and fatigue (14%). There were 6 serious AEs; 1 led to study withdrawal.CONCLUSIONSPatients experienced clinically meaningful improvements in quality of life and pain, without unexpected adverse toxicities. Phase III combination trials of Ra-223 with novel oral hormonal agents are ongoing to further evaluate radiographic progression and overall survival benefit.

22. Immune Analysis of Radium-223 in Patients With Metastatic Prostate Cancer

Author(s): Kim J.W.; Shin M.S.; Kang Y.; Kang I.; Petrylak D.P.

Source: Clinical Genitourinary Cancer; Apr 2018; vol. 16 (no. 2)

Publication Date: Apr 2018

Publication Type(s): Article

Abstract: Background: Radium223 (Ra223) delivers high-energy radiation to osteoblastic metastasis of prostate cancer, resulting in irreparable double-stranded DNA damage. The effects of Ra223 on CD8+ T cell subsets in patients with prostate cancer is unknown. Patients and Methods: Fifteen men with metastatic prostate cancer with clinical indication for Ra223 without any autoimmune or immune deficiency conditions were enrolled. Patients received a course of Ra223 50 kBq/kg. Concurrent use of prednisone <= 10 mg a day was allowed. Peripheral blood samples were collected before and 3 to 4 weeks after the first dose of Ra223 50 kBq/kg. Peripheral blood mononuclear cells were purified and analyzed for the phenotypic and functional characteristics of CD8+ T cells using flow cytometry. Results: One Ra223 treatment did not result in significant change in the overall frequencies of CD8+ T cells and their subsets including naive, central memory, and effect memory cells. However, the mean frequency of programmed cell death protein 1-expressing EM CD8+ T cells decreased after 1 Ra223 treatment from 20.6% to 14.6% (P =.020), whereas no significant change was observed in the frequencies of CD27-, CD28-, or CTLA4-expressing T cells. One Ra223 treatment was not associated with any significant change in the frequencies of CD8+ T cells producing IFN-gamma, TNF-alpha, and IL-13. Conclusion: One Ra223 treatment is associated with a decreased mean frequency of programmed cell death protein 1-expressing effect memory CD8+ T cell without affecting other immune checkpoint molecules or cytokine production. Further investigations are warranted to elucidate the immunologic and clinical significance of our observations and its long-term effects after multiple treatments. Radium-223 delivers high-energy radiation to osseous metastases. Its effect on the immune system is known. We observed a decrease in the mean frequency of programmed cell death protein 1-expressing cytotoxic T cells after 1 treatment of radium-223 in patients with prostate cancer. Further investigation is warranted to define the clinical significance of this finding and to elucidate the immunologic aspect of how radium-223 mediates its anti-tumor activity.

23. Interim analysis of an open label phase ii study of enzalutamide and radium RA 233 dichloride in symptomatic, metastatic castration-resistant prostate cancer patients

Author(s): Shore N.; Harrelson S.; Schellhammer P.; Tutrone R.; Mariados N.

Source: Journal of Urology; Apr 2018; vol. 199 (no. 4)

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract:INTRODUCTION AND OBJECTIVES: We performed a prospective, multicenter, open label trial investigating the safety and tolerability and clinical efficacy of combining Enzalutamide, an androgen receptor inhibitor, with Radium Ra 223 dichloride, a targeted alpha radiotherapy and the combination subsequent effect upon patients with symptomatic, bone metastatic castration-resistant prostate cancer (mCRPC) patients. METHODS: This open-label, phase II study (NCT02507570) enrolled patients with symptomatic bone metastases. Patients were assessed at baseline, day 1 of each of 6 Ra-223 cycles, and 30 days post final RA-223 treatment. The primary objective was safety and tolerability. Secondary objectives included bone pain response via the Bone Pain Index Short Form (BPI-SF), quality of life via the Functional Assessment of Cancer Therapy-Prostate (FACT-P), disease progression, palliative radiotherapy requirement, analgesic advancements, PSA and ALP progression, additional antineoplastic therapy, Eastern Co-operative Oncology Group performance status (ECOG), and overall survival. Data summaries from initiation of RA-223 through 30 day post RA-223 treatment are presented. RESULTS: Of the 39 men ages 70+/-8.2 years that received at least two cycles of RA-223, 34 have completed 6 cycles of RA treatment and are continuing follow-up in this ongoing trial. A total of 10.3% (4/39) of patients reported serious adverse events (AEs) on or after RA-223 initiation, none were related to the treatment, and 53.8%

(21/39) of patients had related non-serious AEs, most commonly fatigue, nausea, anemia/worsening of anemia, and decreased appetite. There were no deaths and no progression requiring additional antineoplastic therapy during this treatment phase. Average BPI-SF pain severity composite improved 0.7 to 1.2 at scheduled visits with RA- 223 administered. Both BPI-SF interference composite and FACT-P quality of life have positive trends but were not statistically significant. ECOG performance status remained consistent. PSA improved 25% and 50% in 62.9% and 40% of patients, respectively, and ALP improved 25% and 50% in 62.9% and 40% of patients, by end of treatment. CONCLUSIONS: This prospective combination trial of Radium 223 and Enzalutamide demonstrates tolerability of use of these approved mCRPC agents with an acceptable safety profile and suggestion of improvement in pain scores, quality of life measures, and maintenance of performance status.

24. Combination therapy with EPI-002 and ionizing radiation for castration-resistant prostate cancer

Author(s): Ito Y.; Banuelos C.A.; Sadar M.D.

Source: Journal of Urology; Apr 2018; vol. 199 (no. 4)

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract:INTRODUCTION AND OBJECTIVES: Targeted radiotherapy with radium 223 dichloride for metastatic castration resistant prostate cancer (mCRPC) increases overall survival (OS) of patients with bone metastases by approximately 3 months. Emerging evidence supports that androgen receptor (AR) signaling regulates DNA repair in prostate cancer. Thus a combination approach using AR modulating drugs with radiation could be a promising option for the treatment of mCRPC. All currently approved AR modulating drugs, such as enzalutamide and abiraterone, either directly or indirectly target the AR C-terminus ligandbinding domain (LBD). Such drugs are often unsuccessful due to the emergence of AR splice variants (ARV-7, ARv567es) that are constitutively active and lack a LBD. EPI-002 is a first-in-class AR antagonist that binds to its N-terminus domain to target both full-length AR and AR splice variants such as AR-V7. Here we present data to support that a combination of EPI-002 and ionizing radiation has beneficial effects in vitro. METHODS: Combination therapy using EPI-002 and ionizing radiation were evaluated in vitro using LNCaP95 human prostate cancer cells. This cell line is androgen-independent, expresses full-length AR and AR-V7, and is resistant to enzalutamide and other antiandrogens. Proliferation was evaluated using BrdU incorporation and colony formation assays. The effects of monotherapy and combination therapy on cell cycle and DNA damage were analysed using FACS and Western blot. RESULTS: Ionizing radiation increased the expression of fulllength AR and AR splice variants and their gene targets, PSA and TMPRSS2. EPI-002 induced G1 cell cycle arrest whereas radiation induced G2/M cell cycle arrest. FACS analysis showed dose-dependent blocking of BrdU incorporation and more accumulation of gammaH2AX in S phase cells in the combination therapy at higher doses of ionizing radiation compared to monotherapy. Combination therapy suggests a synergistic inhibitory effect on proliferation of LNCaP95 cells. CONCLUSIONS: Consistent with previous reports, radiation increased expression of full-length AR expression. Building on these data, here we show for the first time that radiation also increases the expression of AR splice variants thereby implying a possible mechanism of resistance. Hence, combination therapy with radiation and an inhibitor such as EPI-002 that antagonises both AR splice variant and full-length AR, may provide a new therapeutic approach for mCRPC.

25. 2-year follow-up of radium-223 re-treatment in an international, open-label, phase 1/2 study in patients with castration-resistant prostate cancer and bone metastases

Author(s): Mariados N.; Sartor O.; Heinrich D.; Vidal M.J.M.; Keizman D.; Karlsson C.T.; Peer A.; Procopio G.; Frank S.J.; Pulkkanen K.; Rosenbaum E.; Severi S.; Perez J.M.T.; Trandafir L.; Wagner V.; Li R.; Nordquist L.T.

Source: Journal of Urology; Apr 2018; vol. 199 (no. 4)

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract:INTRODUCTION AND OBJECTIVES: Radium-223 (Ra-223) treatment (tx) is indicated for patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (6 x 55 kBq/kg IV injections [inj]; 1 inj q4wk). Early results of an international, open-label, phase 1/2 study (NCT01934790) showed that re-treating patients with Ra-223 was well tolerated with favorable effects on disease progression. Here we report safety and efficacy findings from a 2-year follow-up. METHODS: Patients with CRPC and bone metastases who completed 6 initial Ra-223 inj with no disease progression in bone and later progressed were eligible for Ra-223 re-tx (up to 6 additional Ra- 223 inj), provided that hematologic parameters were adequate. No concomitant cytotoxic agents were allowed; other concomitant agents (eg, abiraterone and enzalutamide) were allowed at investigator discretion. The primary objective was safety. Exploratory objectives included time to radiographic bone progression, radiographic progression- free survival (rPFS), time to total alkaline phosphatase (tALP) and prostate-specific antigen (PSA) progression, overall survival (OS), and time to first symptomatic skeletal event (SSE), all calculated from start of re-tx. The evaluation of safety and exploratory objectives included an active 2-year follow-up. Safety results from the active follow-up period and updated efficacy are reported. RESULTS: 44 patients were re-treated with Ra-223; 29 (66%) completed all 6 inj (median number inj = 6). 34 (77%) of 44 patients entered active follow-up, during which no new safety concerns were noted. One new primary malignancy was reported (basal cell carcinoma; not considered related to study drug). There were no serious drug-related adverse events. 19 (43%) of 44 patients had an rPFS event (radiographic progression or death); median rPFS was 9.9 months. Only 5 (11%) of 44 patients had radiographic bone progression; median time to radiographic bone progression was not reached. Median time to tALP progression was not reached, median time to PSA progression was 2.2 months. Median OS was 24.4 months. Median time to first SSE was 16.7 months. CONCLUSIONS: Re-treating patients with Ra-223 was well tolerated in this select population, led to minimal hematologic toxicity, and provided continued disease control in bone at the 2-year follow-up.

26. Pre-treatment stratification of patients receiving radium-223 dichloride for bone metastases from castration-resistant prostate cancer

Author(s): Kenning L.; Wright G.; Dixit S.; Beavis A.

Source: Nuclear Medicine Communications; Apr 2018; vol. 39 (no. 4); p. 372

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract: Purpose: Identify prognostic biomarkers in hormonerelapsed prostate cancer patients with bone metastases undergoing Radium-223 dichloride (Ra-223) treatment. Background: As a relatively new treatment, identification of patients suitable for Ra-223 dichloride (Xofigo) is still being determined. Current selection criteria utilise performance score and haemoglobin (Parker C. 2013. N Engl J Med; 369:213-223), however, this may not accurately represent the extent of disease and most suitable candidates. This retrospective audit investigated the predictive value of other pre-treatment biomarkers to help identify patients likely to benefit from Ra-223 treatment. Methods: All patients who had received at least 1 cycle of Ra-223 were included. Administered dose, compliance, toxicity, biochemical blood profiles, performance status, pain, previous treatments and survival were recorded. Continuous variables were dichotomised using median values prior to Kaplan-Meier

Survival Analysis. Cox regression survival analysis was performed using a Backwards-Wald methodology. Results: 55 patients (34 patients (62%)-6 cycles, 21 patients-1-5 cycles) had finished Ra-223 treatment between 30/12/2014 and 01/01/2017. Censor date was 20/09/2017. Significant pre-treatment predictors of improved survival were: PSA <108.3 mu g/litre, ALP <146 mu l, Lymphocytes =1.4 mu l, Neutrophil/Lymphocyte< 3.18. Pre-treatment Docetaxel status, PSA, ALP, Neutrophil and Lymphocyte measurements were independent predictors of survival following Cox regression analysis. Post-treatment PSA, ALP and 6 cycle completion status were significant survival predictors after Cox regression analysis. Pain scores were not documented; however, 28/37 patients reported reduced pain. Conclusion: Docetaxel status, PSA, ALP, Neutrophil and Lymphocyte measurements were stronger predictors than performance score and haemoglobin at stratifying patients who could benefit from Ra-223.

27. Radium-223 therapy at a tertiary referral centre: Review of referral and treatment trends over a 4 year period

Author(s): Jarvis P.; Vigneswaran G.; Basketter V.; Sundram F.

Source: Nuclear Medicine Communications; Apr 2018; vol. 39 (no. 4); p. 373-374

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract: Background: Radium-223 therapy for bony metastatic castration resistant prostate cancer (mCRPC) prolongs overall survival, improves quality of life, is NICE approved and commissioned by NHS England. The course of treatment consists of 6 cycles, administered intravenously every 4 weeks. We introduced the nuclear medicine led radium service at our centre in 2014. We evaluated our referral and treatment trends over a 4 year period. Method: Retrospective review of our departmental radium database, with analysis of referrals and treatments over a 44 month period (January 2014 to September 2017). Results: In total, there were 179 referrals and 589 treatments to date. Referral volumes increased from 31 in 2014, 58 in 2015, 45 in 2016 and 45 in 2017 to date (65 projected for entire 2017). Treatment volumes also increased from 67 in 2014, 194 in 2015, 186 in 2016 and 142 in 2017 to date (213 projected for entire 2017). The 2016 dip was due to uncertainty around NICE appraisal outcomes and commissioning approval. The increased demand has resulted in increased time from referral to first clinic appointment (2014 = 14.6 days vs. 2017 = 19.0 days). Conclusion: Radium-223 referrals and treatments have increased over the past 4 years. To address the increased demand and to maintain high quality, timely service provision, it is vital to ensure adequate workforce and resource planning. The increased time between referral and first clinic appointment may result in treatment commencement delays, which could negatively impact on patients who already have limited survival.

28. Does prior chemotherapy affect the number of radium-223 therapy cycles completed and post radium therapy survival?

Author(s): Jarvis P.; Vigneswaran G.; Basketter V.; Sundram F.

Source: Nuclear Medicine Communications; Apr 2018; vol. 39 (no. 4); p. 373

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract: Background: NICE guidelines recommend radium-223 therapy for symptomatic bony metastatic castration resistant prostate cancer (mCRPC) patients who had previous chemotherapy or when chemotherapy is contraindicated or not suitable. The full course of 6 radium therapy cycles improves overall survival, however not all patients are able to complete 6 cycles. We investigated

whether prior chemotherapy affected both the number of radium therapy cycles completed and also survival following radium therapy. Method: Retrospective study of all patients undergoing radium therapy over a 44 month period (January 2014-September 2017). Clinical notes were reviewed to determine prior chemotherapy status. The number of radium therapy cycles completed and survival duration post first cycle were evaluated. Results: 123 patients had radium therapy; of whom 66 (54%) had no previous chemotherapy and 57 (46%) had previous chemotherapy. A greater proportion of patients with no previous chemotherapy (43/66 = 65%) completed 6 cycles of radium therapy, when compared to patients who had previous chemotherapy (26/57 = 46%) (P = 0.029). There was however, no significant difference in survival between these 2 groups (median survival: previous chemotherapy = 518 days vs. no previous chemotherapy = 590 days; P = > 0.05). Conclusion: Patients who did not have chemotherapy prior to radium therapy were more likely to complete the full 6 cycles of radium therapy. These patients may be fitter and more likely to tolerate treatment. However, there was no significant difference in survival duration following radium therapy, whether or not they had received previous chemotherapy.

29. Prognostic value of PSA as a marker for survival in bony metastatic castration resistant prostate cancer patients receiving radium-223 therapy

Author(s): Vigneswaran G.; Jarvis P.; Sundram F.

Source: Nuclear Medicine Communications; Apr 2018; vol. 39 (no. 4); p. 373

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract: Background and Aims: Evidence for the survival benefit of Radium-223 therapy in bony metastatic castration resistant prostate cancer (mCRPC) is well-established. However, there remains no clear consensus regarding prognostic markers for survival. We investigated the relationship between PSA (prostate specific antigen) and survival and assessed whether PSA could be used as a prognostic marker in patients receiving Radium-233 therapy. Method: Retrospective study over a 42 month period (March 2014-September 2017). Data was obtained from the Wessex MDT database and UHS electronic patient records. PSA levels before and after the recommended 6 cycles of radium therapy were noted. Linear regression analysis (robust fit) was used to assess the relationship and outliers were removed from the regression analysis. Results: Of 65 patients who completed 6 cycles of radium therapy, data was available for 21 patients. The median PSA after and prior to therapy was 170 ng/ml and 120 ng/ml respectively. Robust linear regression analysis demonstrates a statistically significant inversely proportional relationship between rise in PSA and survival. The resulting fitted linear regression line was given by; Survival (days) =-0.64 PSA difference + 518, (R2 = 0.3, P = 0.02). Conclusion: We propose linear regression to model survival based on change in PSA. A fall or less dramatic rise in PSA level is associated with a proportional increase in survival and therefore PSA could be used as a prognostic marker for survival. PSA measurements at predetermined time points should be considered in those receiving Radium-223 therapy for bony mCRPC.

30. Survival benefit of radium-223 therapy for bony metastatic castration resistant prostate cancer

Author(s): Vigneswaran G.; Jarvis P.; Sundram F.

Source: Nuclear Medicine Communications; Apr 2018; vol. 39 (no. 4); p. 372

Publication Date: Apr 2018

Publication Type(s): Conference Abstract

Abstract: Background and Aims: The use of Radium-223 therapy for bony metastatic castration resistant prostate cancer (mCRPC) has increased due to improved access and strong evidence base.

We reviewed the survival benefit of this therapy in our patient cohort. Method: Retrospective analysis over 42 months (March 2014-September 2017) of all patients who were administered radium therapy. Patient information was obtained from the Wessex MDT database and UHS electronic patient records. Kaplan-Meier survival curves and hazard ratios were calculated to quantify the effect of therapy on overall survival (OS) for patients who completed the recommended 6 treatment cycles versus patients who did not. We also evaluated the survival benefit in relation to the number of treatment cycles completed. Results: 129 patients were identified. The median OS for those who completed 6 cycles (n = 65) was 802 days versus 288 days for those who completed less than 6 cycles (n = 64). There was a statistically significant OS benefit for those who completed 6 cycles ($P < 0.01$, hazard ratio 0.31). Further analysis, using a multi-way ANOVA showed an increasing survival benefit in relation to the number of therapy cycles completed ($P = 0.0008$), particularly following completion of 3 cycles. Conclusion: Radium-223 therapy has a significant survival benefit and OS increases with the number of treatment cycles completed. There may be concerns regarding patient suitability for mCRPC therapies. For patients in whom mCRPC therapy might otherwise not have been considered, the survival benefit of radium therapy is a vital consideration when appropriate patients are offered treatment.

31. Hematologic Toxicity From Radium-223 Therapy for Bone Metastases in Castration-Resistant Prostate Cancer: Risk Factors and Practical Considerations.

Author(s): Jacene, Heather; Gomella, Leonard; Yu, Evan Y; Rohren, Eric M

Source: Clinical genitourinary cancer; Mar 2018

Publication Date: Mar 2018

Publication Type(s): Journal Article Review

PubMedID: 29678471

Abstract: Radium-223 dichloride is an α-emitting radiopharmaceutical that localizes to bone matrix and is approved for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) and symptomatic bone metastases. The cumulative impact of Ra-223 and other therapeutic agents for metastatic CRPC on myelosuppression in bone marrow is unknown. The phase 3 randomized, double-blind, placebo-controlled ALSYMPCA trial of Ra-223 in patients with CRPC and symptomatic bone metastases demonstrated a significant improvement in overall survival. Of the 571 patients subsequently followed for 3 years, few in either the Ra-223 or placebo arm experienced hematologic adverse events. Little evidence shows secondary malignancies associated with Ra-223 treatment; only 2 cases of secondary leukemia after Ra-223 treatment were found in the literature. The goals of this review were to summarize safety and efficacy results from clinical trials and institutional safety data pertaining to hematologic adverse events occurring with Ra-223, and to discuss practical management issues.

32. Current treatment strategies for advanced prostate cancer.

Author(s): Komura, Kazumasa; Sweeney, Christopher J; Inamoto, Teruo; Ibuki, Naokazu; Azuma, Haruhito; Kantoff, Philip W

Source: International journal of urology : official journal of the Japanese Urological Association; Mar 2018; vol. 25 (no. 3); p. 220-231

Publication Date: Mar 2018

Publication Type(s): Journal Article Review

PubMedID: 29266472

Abstract: During the past decade, treatment strategies for patients with advanced prostate cancer involving stage IV (T4N0M0, N1M0 or M1) hormone-sensitive prostate cancer and recurrent prostate cancer after treatment with curative intent, as well as castration-resistant prostate cancer, have extensively evolved with the introduction and approval of several new agents including sipuleucel-T, radium-223, abiraterone, enzalutamide and cabazitaxel, all of which have shown significant improvement on overall survival. The appropriate use of these agents and the proper sequencing of these agents are still not optimized. The results of several recently reported randomized controlled trials and retrospective studies could assist in developing a treatment strategy for advanced prostate cancer. In addition, prospective studies and molecular characterization of tumors to address these issues are ongoing.

33. The next generation of radioimmunotherapy: Targeted alpha therapy (TAT)

Author(s): Molnar I.; Burak E.; Forbes J.; Simms R.; Valliant J.

Source: Annals of Oncology; Mar 2018; vol. 29

Publication Date: Mar 2018

Publication Type(s): Conference Abstract

Abstract: Targeted alpha therapy (TAT) involves selective delivery of isotopes that emit highly energetic alpha particles to cancer cells leading to their ultimate destruction, while minimizing collateral damage to healthy surrounding cells. The high linear energy transfer of alpha particles makes it possible to consider targets with relatively low cellular expression levels (or concentration) and to treat hypoxic and chemotherapy resistant tumors. The limited emission of beta and gamma radiation from the appropriate alpha emitting isotopes significantly reduces the complexities of administration and decreases the chance of exposure to caregivers and family members. Despite the potential, clinical development of targeted alpha therapeutics has been slow due to a variety factors that will be discussed. Radium-223 dichloride, the only approved alpha therapy in clinical medicine, provides the proof of concept for internal alpha emitting radioisotope therapy in cancer treatment. 223RaCl2 is "targeted" via its fundamental physicochemical properties as it incorporates into the bone matrix at sites of bone formation. The interest in TAT is based partly on the clinical usefulness of 223RaCl2 in castration resistant prostate cancer. However, 223RaCl2 is only suitable for treating bone metastases, so new targeted therapies that aim to treat liquid and solid soft tissue tumors are now under clinical development. The clinical experience to date with TAT will be reviewed focusing on the status, advantages and disadvantages of different radioisotope payloads (213Bi, 225Ac, 211At, 212Pb and 227Th), targets (CD33, CD20, CD22, PSMA, HER2, somatostatin receptor and others), and targeting agents (small molecules, peptide and antibodies) that have been employed to date. The momentum in the TAT field is illustrated by a growing number of promising TAT compounds that are in or near starting clinical trials. The current status of these TAT molecules (225Ac-PSMA-617, 212Pb-AR-RMX, 225Ac-lintuzumab, FPX-01, 211At-BC8-B10, BAY1862864) will be discussed with particular attention to those agents that use 225Ac (t1=2 10 days) and 227Th (t1=2 18.7 days) as the therapeutic payload. The half-life of these two alpha emitting isotopes permits manufacturing and delivery of ready-to-use doses to patients. Biodistribution and dosimetry may require the use of a separate imaging radioimmunoconjugate when alpha isotopes with limited gamma emission are used. The potential role of TAT in hematological malignancies and in solid tumor treatment will also be discussed along with systemic and local administrations strategies, both of which may prove to have clinical utility in coming years.

34. Radium-223 re-treatment in patients with castration-resistant prostate cancer and bone metastases: 2-year follow-up from an international, open-label, phase 1/2 study

Author(s): Heinrich D.; Nordquist L.; Mariados N.; Mendez Vidal M.J.; Keizman D.; Thellenberg Karlsson C.; Peer A.; Procopio G.; Frank S.; Pulkkanen K.; Rosenbaum E.; Severi S.; Trigo Perez J.M.; Trandafir L.; Wagner V.; Li R.; Sartor O.

Source: European Urology, Supplements; Mar 2018; vol. 17 (no. 2)

Publication Date: Mar 2018

Publication Type(s): Conference Abstract

Abstract: Introduction & Objectives: Radium-223 (Ra-223) treatment (tx) is indicated for patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) (6 x 55 kBq/kg IV injections [inj]; 1 inj q4wk). Early results of an international, open-label, phase 1/2 study (NCT01934790) showed that re-treating patients with Ra-223 was well tolerated with favorable effects on disease progression. Here we report safety and efficacy findings from a 2-year follow-up. Materials & Methods: Patients with CRPC and bone mets who completed 6 initial Ra-223 inj with no disease progression in bone and later progressed were eligible for Ra-223 re-tx (6 additional Ra-223 inj), provided that hematologic parameters were adequate. No concomitant cytotoxic agents were allowed; other concomitant agents (eg, abiraterone and enzalutamide) were allowed at investigator discretion. The primary objective was safety. Exploratory objectives were time to radiographic bone progression, radiographic progression-free survival (rPFS), overall survival (OS), time to first symptomatic skeletal event (SSE), and SSE-free survival, all calculated from start of re-tx. An active 2-year follow-up evaluated safety and exploratory objectives. Safety results from the active follow-up period and updated efficacy are reported. Results: 44 patients were re-treated with Ra-223; 29 (66%) completed all 6 inj (median number inj = 6). 34 (77%) of 44 patients entered active follow-up, during which no new safety concerns were noted. One adverse event (AE) reported during follow-up was considered related to study drug (grade 3 anemia). One new primary malignancy was reported (basal cell carcinoma; not considered related to study drug). There were no serious drug-related AEs. At the end of active follow-up, 2 (6%) of 34 patients had grade 1 anemia; no patients had any grade neutropenia or thrombocytopenia. Changes in hematologic lab values over time will be presented. 19 (43%) of 44 patients had an rPFS event (radiographic progression or death); median rPFS was 9.9 months. Only 5 (11%) of 44 patients had radiographic bone progression; median time to radiographic bone progression was not reached. Median OS was 24.4 months. Median time to first SSE and SSE-free survival were 16.7 and 12.8 months, respectively. Conclusions: Re-treating patients with Ra-223 was well tolerated in this select population, led to minimal hematologic toxicity, and provided continued disease control in bone at the 2-year follow-up.

35. REASSURE observational study of radium-223 (Ra-223): First interim results by prior/ concomitant treatment (Tx) in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) enrolled in Europe

Author(s): Logue J.; Schostak M.; Baldari S.; Schrijvers D.; Sandzen J.; Meidahl Petersen P.; Procopio G.; Straus A.; Borrega P.; Rebmann U.; Miller K.; Kalinovsky J.; De Sanctis Y.; Sternberg C.; Tombal B.

Source: European Urology, Supplements; Mar 2018; vol. 17 (no. 2)

Publication Date: Mar 2018

Publication Type(s): Conference Abstract

Abstract: Introduction & Objectives: The ALSYMPCA trial (3 yr follow-up) demonstrated a favourable safety profile and extended survival in pts with mCRPC treated with Ra-223, a targeted alpha therapy.1 REASSURE will evaluate long-term safety (7 yr follow-up) of Ra-223 in clinical practice. Materials & Methods: The global, prospective, single-arm, observational REASSURE study enrolled

pts with mCRPC with bone metastases (mets) planned to receive Ra-223. We conducted a descriptive analysis of safety and characteristics of pts enrolled in Europe based on concomitant and prior txs, using data from the first planned interim analysis (pts receiving >=1 Ra-223 dose; median follow-up 6 mo). Results: The analysis included 339 pts; 22% had extraskeletal disease at baseline. Pts who received fewer lines of therapy had lower median baseline PSA and ALP and were more likely to complete Ra-223 tx (Table). Drug-related treatment-emergent AEs (TEAEs) occurred in 144 pts (42%), most commonly diarrhoea, nausea and anaemia. Drug-related serious AEs occurred in 17 (5%) pts; TEAEs led to permanent tx discontinuation in 26 (8%). TEAE incidence was not increased by prior or concomitant txs. Conclusions: In routine clinical practice in Europe, Ra-223 had a good short-term safety profile; prior or concomitant txs did not appear to increase TEAE incidence. Pts with fewer tx lines before Ra-223 had higher Ra-223 tx completion rates, which may reflect lower disease burden, as suggested by lower median baseline PSA, ALP, and extent of disease. 1. NEJM 2013;369:213-23. (Table presented) .

36. Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial

Author(s): Parker C.C.; Coleman R.E.; Sartor O.; Vogelzang N.J.; Bottomley D.; Heinrich D.; Helle S.I.; O'Sullivan J.M.; Fossa S.D.; Chodacki A.; Wiechno P.; Logue J.; Seke M.; Widmark A.; Johannessen D.C.; Hoskin P.; James N.D.; Solberg A.; Syndikus I.; Kliment J.; Wedel S.; Boehmer S.; Dall'Oglio M.; Franzen L.; Bruland O.S.; Petrenciuc O.; Li R.; Staudacher K.; Nilsson S.

Source: European Urology; Mar 2018; vol. 73 (no. 3); p. 353-360

Publication Date: Mar 2018

Publication Type(s): Article

Abstract: Background: In Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, radium-223 versus placebo prolonged overall survival with favorable safety in castration-resistant prostate cancer patients with symptomatic bone metastases. Long-term radium-223 monitoring underlies a comprehensive safety and risk/benefit assessment. Objective: To report updated ALSYMPCA safety, including long-term safety up to 3 yr after the first injection. Design, setting, and participants: Safety analyses from phase 3 randomized ALSYMPCA trial included patients receiving >=1 study-drug injection (600 radium-223 and 301 placebo). Patients (405 radium-223 and 167 placebo) entered long-term safety follow-up starting 12 wk after the last study-drug injection, to 3 yr from the first injection. Forty-eight of 405 (12%) radium-223 and 12/167 (7%) placebo patients completed follow-up, with evaluations every 2 mo for 6 mo, then every 4 mo until 3 yr. Outcome measurements and statistical analysis: All adverse events (AEs) were collected until 12 wk after the last injection; subsequently, only treatment-related AEs were collected. Additional long-term safety was assessed by development of acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic anemia, and secondary malignancies. Data analysis used descriptive statistics. Results and limitations: During treatment to 12 wk following the last injection, 564/600 (94%) radium-223 and 292/301 (97%) placebo patients had treatment-emergent AEs (TEAEs). Myelosuppression incidence was low. Grade 3/4 hematologic TEAEs in radium-223 and placebo groups were anemia (13% vs 13%), neutropenia (2% vs 1%), and thrombocytopenia (7% vs 2%). Ninety-eight of 600 (16%) radium-223 and 68/301 (23%) placebo patients experienced grade 5 TEAEs. Long-term follow-up showed no AML, MDS, or new primary bone cancer; secondary non-treatment-related malignancies occurred in four radium-223 and three placebo patients. One radium-223 patient had aplastic anemia 16 mo after the last injection. No other cases were observed. Limitations include short (3-yr) follow-up. Conclusions: Final long-term safety ALSYMPCA analysis shows that radium-223 remained well tolerated, with low myelosuppression incidence and no new safety concerns. Patient summary: Updated Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial findings show that radium-

223 remained well tolerated during treatment and up to 3 yr after each patient's first injection. Three-year safety follow-up of Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial patients with castration-resistant prostate cancer and symptomatic bone metastases revealed a continued low incidence of myelosuppression, minimal nonhematologic adverse events, and secondary malignancies (none related to treatment) in four radium-223 patients and three placebo patients.

37. First results from the ADRRAD trial e combination androgen deprivation therapy (ADT), whole pelvis radiotherapy (WPRT) and radium 223 in recently diagnosed metastatic hormone sensitive prostate cancer (MHSPCa)

Author(s): Turner P.G.; Jain S.; O'Sullivan J.M.; Mitchell D.M.; Hounsell A.; Biggart S.

Source: Clinical Oncology; Mar 2018; vol. 30 (no. 3); p. 196

Publication Date: Mar 2018

Publication Type(s): Conference Abstract

Abstract: Aims: The upfront use of systemic agents in MHSPCa, namely abiraterone [1] and docetaxel [2], improves survival; prostate radiotherapy in metastatic PCa may improve survival [3]. The ADRRAD trial seeks to establish the safety and any signal of efficacy associated with upfront radium 223 and concurrent WPRT in patients with MHSPCa, in addition to standard ADT. Methods: Eligible patients had MHSPCa, minimum 3 bone metastases, absence of visceral metastases and PS 0e1. Patients could receive upfront docetaxel pre-trial. Patients were treated with continuing ADT, 6 cycles of radium 223 at 55 kBq/kg and VMAT to pelvis aiming for 74 Gy in 37 fractions to prostate and 60 Gy in 37 fractions to lymph node bed. WPRT and radium 223 ran concurrently e fraction 1 WPRTcoincided with D1C1 radium 223. Patients were assessed at each visit with PSA, ALP, AEs by CTCAE4.03, EPIC QoL questionnaire and translational bloodwork. Whole body MRI was performed at outset, after completion of radionuclide therapy, and again 6 months later. Results: 20 patients of a planned 30 have been recruited. These results concern the first 10 patients treated, median follow-up post-C1D1 is 29 weeks. 8 patients received pre-study docetaxel. In total, 168 AEs have occurred, 70.2% grade 1, 25.6% grade II and 4.2% grade III. Commonest AE = leucopenia, grade I on 10 occasions, grade II on 13 occasions and grade III on 2 occasions. Diarrhoea was relatively common, but low grade; grade 1 on 15 occasions, grade 2 on 4 occasions. 4 SAEs have occurred: 1 episode of pyrexia possibly related to radium 223 infusion, 1 episode of UTI possibly related to WPRT, 2 SAEs were unrelated to study treatments. 9 patients had evaluable pairs of WBMRI pre-and post-radium 223/WPRT. 1 showed PD, 1 showed mixed response, 7 showed PR. Conclusion: A strong signal of tolerability and marked radiological improvement on WBMRI (even post-docetaxel) is emerging.

38. Radium 223: Experience of the first 100 patients in a regional centre

Author(s): Thompson M.K.; Lynskey D.M.; Patel L.; Buscombe J.; Russell S.

Source: Clinical Oncology; Mar 2018; vol. 30 (no. 3); p. 196

Publication Date: Mar 2018

Publication Type(s): Conference Abstract

Abstract: Aims: The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study established radium 223 as an effective treatment in men with castration-resistant prostate cancer and bone metastases [1]. The authors analysed outcomes for patients who had received radium 223 at Addenbrooke's Hospital, Cambridge, UK. Methods: We performed a retrospective review of electronic health records of all men treated with radium 223 between 1 January 2015 and 30 June 2017. Age, performance status, number of cycles completed, alkaline phosphatase and prostate specific antigen (PSA) levels before and after first and last treatments, reasons for not completing

treatment course and date of death were recorded. Statistical analysis was conducted using Excel and Prism. Results: 112 records were reviewed, 8 were excluded as treatment was ongoing, giving n = 104. The median age was 73 years (range 56e93). Performance status, recorded for 51 patients, revealed 20 had PS 0 (39%), 21 had PS 1 (41%), 8 had PS 2 (16%) and 2 had PS 3 (4%). 58 patients (56%) completed all 6 cycles of treatment and 46 patients (44%) did not for the following reasons: clinical deterioration/progressive disease (18/46), bone pain (6/46), bone marrow toxicity (3/46), diarrhoea (2/46), nausea (2/46), death (4/46), other toxicity (1/46). 10/46 patients had no reason recorded. 42 patients had pre-and post-treatment alkaline phosphatase values. The median change in alkaline phosphatase was e55 IU/l (range e1234 to +271 IU/l). 41 patients had pre-and post-treatment PSA values. The median change in PSA was +32 ng/ml (range e966 to +1719 ng/ml). The median overall survival for all patients from the commencement of radium 223 was not reached. 72.3% of patients survived 1 year, with 44 the number of patients at risk at 1 year. Conclusion: Radium 223 is an effective and safe treatment in the setting of a regional UK centre.

39. Radium 223 therapy in symptomatic metastatic castrate resistant prostate cancer e newcastle experience: A quality of life issue

Author(s): Jiang X.Y.; Frew J.; McMenemin R.; Pedley I.; Atkinson S.; Leaning D.

Source: Clinical Oncology; Mar 2018; vol. 30 (no. 3); p. 194

Publication Date: Mar 2018

Publication Type(s): Conference Abstract

Abstract: Aims: Radium 223 (Ra223) is an alpha particle radiopharmaceutical used in the treatment of men with symptomatic bone metastasis secondary to castration resistant prostate cancer without visceral disease. The ALSYMPCA phase III trial has demonstrated that Ra223 improves both survival and disease-related quality of life (QoL) compared with placebo [1]. The Northern Centre for Cancer Care was one of the first UK centres to offer Ra223 in 2014. Our data (n = 143) previously demonstrated that patients who completed all 6 cycles of treatment survive longer than those who did not (median 12.4 months versus4.7 months, HR0.33; P = 0.0001)[2]. We reportfor the first time QoL outcomes of some of these patients based on patient-reported outcome measures, which have been implemented since August 2015. Methods: We prospectively collected data using an abbreviated Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, which patients fill in prior to each treatment. Records of patients who finished the course between August 2015 and July 2017 were analysed. Results: In total, 54 patients completed the QoL questionnaires, with 65% (35) of patients completing 6 cycles,19% (10) received 5 cycles, 6% (3) 4 cycles and 10% (6) 3 cycles. Overall, 59% (32) of patients had improvement of their total physical well-being scores including pain, of these 88% managed 5 cycles or more. 15% (8) had no change and 26% (14) had worsening of their scores e a risk ratio of 1.8 for those who did not complete all 6 treatments. Conclusion: Ra223 improves disease related QoL and reduces pain in this group of patients. 5 or more treatments may be required to benefit. This is consistent with our previous finding on survival benefit. Interim worsening of QoL is more likely if fewer treatments were given. Ra223 should only be offered to patients who are fit to complete the 6 months course of treatment.

40. Radium-223 Safety, Efficacy, and Concurrent Use with Abiraterone or Enzalutamide: First U.S. Experience from an Expanded Access Program.

Author(s): Sartor, Oliver; Vogelzang, Nicholas J; Sweeney, Christopher; Fernandez, Daniel C; Almeida, Fabio; Iagaru, Andrei; Brown, Alan; Smith, Matthew R; Agrawal, Manish; Dicker, Adam P; Garcia, Jorge A; Lutzky, Jose; Wong, Yu-Ning; Petrenciuc, Oana; Gratt, Jeremy; Shore, Neal D; Morris, Michael J; U.S. Expanded Access Program Investigators

Source: The oncologist; Feb 2018; vol. 23 (no. 2); p. 193-202

Publication Date: Feb 2018

Publication Type(s): Journal Article

PubMedID: 29183960

Available at The Oncologist - from EBSCO (MEDLINE Complete)

Abstract:BACKGROUNDIn the phase III ALSYMPCA trial, metastatic castration-resistant prostate cancer (mCRPC) patients had few prior life-prolonging therapies. Following ALSYMPCA, which demonstrated radium-223 survival benefit, and before radium-223 U.S. commercial availability, an expanded access program (EAP) providing early-access radium-223 allowed life-prolonging therapies in current use.SUBJECTS, MATERIALS, AND METHODSThis phase II, open-label, single-arm, multicenter U.S. EAP (NCT01516762) enrolled patients with symptomatic mCRPC, ≥2 bone metastases, and no lung, liver, or brain metastases. Patients received radium-223 55 kBq/kg intravenously every 4 weeks × 6. Primary outcomes were acute and long-term safety. Additional analyses were done by number of radium-223 injections, and prior or concomitant abiraterone or enzalutamide use.RESULTSOf 252 patients, 184 received radium-223: 165/184 (90%) had Eastern Cooperative Oncology Group (ECOG) performance status 0-1; 183 (99%) had prior systemic anticancer therapy. Treatment-related adverse events occurred in 93/184 (51%) patients during treatment and 11 (6%) during follow-up. Median overall survival was 17 months, with 134/184 (73%) patients censored because of short follow-up due to radium-223 approval. In post hoc analyses, patients with ≥3 prior anticancer medications, baseline ECOG performance status ≥2, and lower baseline hemoglobin were less likely to receive 5-6 radium-223 injections and unlikely to benefit from radium-223. Radium-223 was well tolerated regardless of concurrent or prior abiraterone or enzalutamide.CONCLUSIONRadium-223 was well tolerated, with no new safety concerns; safety was maintained with abiraterone or enzalutamide. Patients with more advanced disease were less likely to benefit from radium-223. Clinicians should consider baseline characteristics and therapy sequence for greatest clinical value.IMPLICATIONS FOR PRACTICEIn this phase II U.S. expanded access program, radium-223 was well tolerated, with a median overall survival of 17 months in metastatic castration-resistant prostate cancer patients. In post hoc analyses, radium-223 was safe regardless of concurrent abiraterone or enzalutamide, and median overall survival appeared longer when radium-223 was used earlier in patients with less prior treatment. Patients with more advanced disease were less likely to benefit from radium-223. Clinicians should consider baseline clinical characteristics and therapy sequence to provide the greatest clinical value to patients.

41. Excretion and whole-body retention of radium-223 dichloride administered for the treatment of bone metastases from castration resistant prostate cancer.

Author(s): Pratt, Brenda E; Hindorf, Cecilia; Chittenden, Sarah J; Parker, Christopher C; Flux, Glenn D

Source: Nuclear medicine communications; Feb 2018; vol. 39 (no. 2); p. 125-130

Publication Date: Feb 2018

Publication Type(s): Journal Article

PubMedID: 29189490

Abstract:OBJECTIVEThe aim of the study was to determine the fraction of administered activity that was excreted and retained by a small cohort of patients who each received treatment with radium-223 dichloride (Ra). Ra is an α-emitting radionuclide that has been approved for use in the treatment of bone metastases that are secondary to castration resistant prostate cancer.PATIENTS AND METHODSSix patients received two weight-based administrations of Ra 6 weeks apart. Activity excreted in the urine and faeces during the first 48 h following each treatment was assessed by direct counting of the excreta. During the same period the whole-body retention of Ra was also

determined using a single probe counting system. The results of the excreta counting and the whole-body counting were compared to determine whether whole-body counting was a suitable surrogate for assessing excretion. Further whole-body retention counts were made at around 3, 4, 7 and 42 days following treatment.RESULTSPatterns of excretion and retention of Ra varied significantly between patients, but were similar for each patient's pair of treatments. The cumulative maximum activity excreted in the initial 8-h period following the Ra administration was 2.6% that increased to 39% at 48 h. The median excreted activity at ~1 and 6 weeks after treatment was 70 and 86%, respectively. Skeletal retention of Ra at 6 weeks ranged from 11 to 60% of the administered activity.

42. Phase II study of radium-223 dichloride in Japanese patients with symptomatic castration-resistant prostate cancer.

Author(s): Matsubara, Nobuaki; Nagamori, Satsohi; Wakumoto, Yoshiaki; Uemura, Hirotsugu; Kimura, Go; Yokomizo, Akira; Kikukawa, Hiroaki; Mizokami, Atsushi; Kosaka, Takeo; Masumori, Naoya; Kawasaki, Yoshihide; Yonese, Junji; Nasu, Yasutomo; Fukasawa, Satoshi; Sugiyama, Takayuki; Kinuya, Seigo; Hosono, Makoto; Yamaguchi, Iku; Tsutsui, Hirokazu; Uemura, Hiroji

Source: International journal of clinical oncology; Feb 2018; vol. 23 (no. 1); p. 173-180

Publication Date: Feb 2018

Publication Type(s): Journal Article

PubMedID: 28770408

Available at International Journal of Clinical Oncology - from PubMed Central

Abstract:BACKGROUNDRadium-223 dichloride (radium-223) is the first targeted alpha therapy approved for the treatment of castration-resistant prostate cancer (CRPC) with bone metastases. This study investigated the efficacy and safety of radium-223 in Japanese patients with symptomatic CRPC and bone metastases.METHODSIn this open-label, multicenter, phase II study, patients with progressive, symptomatic CRPC and bone metastases were treated with radium-223 (55 kBq/kg, intravenously) in a 4-week cycle for six cycles. The primary endpoint was the percent change in total alkaline phosphatase (ALP) from baseline at 12 weeks. Secondary endpoints included the percent ALP change from baseline to end of treatment (EOT), ALP response rates, percent change in prostate-specific antigen (PSA) from baseline to 12 weeks and EOT, PSA response rates, overall survival (OS), and time to symptomatic skeletal events (SSEs). Adverse events were monitored throughout the study period.RESULTSOf the 49 Japanese patients (median age 74 years), 28 completed all infusions. Mean percent change in total ALP and PSA from baseline to 12 weeks was -19.3 and +97.4%, respectively. One-year OS and SSE-free rate at the end of active follow-up were 78 and 89%, respectively. The ALP response rate was 31%, while the PSA response rate was 6%. Grade 3/4 treatment-emergent adverse events observed in ≥10% of patients included decreased lymphocyte count (14%), anemia (14%), anorexia (10%), and bone pain (10%).CONCLUSIONSRadium-223 is effective and well tolerated in Japanese patients with CRPC and bone metastases. Results were comparable with the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial.CLINICAL TRIAL REGISTRATIONClinicalTrials.gov NCT01929655.

43. Dutch Economic Value of Radium-223 in Metastatic Castration-Resistant Prostate Cancer.

Author(s): Peters, Michel L; de Meijer, Claudine; Wyndaele, Dirk; Noordzij, Walter; Leliveld-Kors, Annemarie M; van den Bosch, Joan; van den Berg, Pieter H; Baka, Agni; Gaultney, Jennifer G

Source: Applied health economics and health policy; Feb 2018; vol. 16 (no. 1); p. 133-143

Publication Date: Feb 2018

Publication Type(s): Journal Article

PubMedID: 28866822

Available at Applied Health Economics and Health Policy - from International DOI Foundation

Abstract:BACKGROUNDThe treatment of metastatic castration-resistant prostate cancer has changed with the introduction of radium-223, cabazitaxel, abiraterone and enzalutamide. To assess value for money, their cost effectiveness in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel from the Dutch societal perspective was investigated.METHODSA cost-effectiveness analysis was conducted using efficacy, symptomatic skeletal-related event and safety data obtained from indirect treatment comparisons. Missing skeletal-related event data for cabazitaxel were conservatively assumed to be identical to radium-223. A Markov model combined these clinical inputs with Dutch-specific resource use and costs for metastatic castration-resistant prostate cancer treatment from a societal perspective. Total quality-adjusted life-years and costs in 2017 euros were calculated over a 5-year (lifetime) time horizon.RESULTSRadium-223 resulted in €6092 and €4465 lower costs and 0.02 and 0.01 higher quality-adjusted life-years compared with abiraterone and cabazitaxel, respectively, demonstrating dominance of radium-223. Sensitivity analyses reveal a 64% (54%) chance of radium-223 being cost effective compared with abiraterone (cabazitaxel) at the informal €80,000 willingness-to-pay threshold. Compared with enzalutamide, radium-223 resulted in slightly lower quality-adjusted life-years (-0.06) and €7390 lower costs, revealing a 61% chance of radium-223 being cost effective compared with enzalutamide. The lower costs of radium-223 compared with abiraterone and enzalutamide are driven by lower drug costs and prevention of expensive skeletal-related events. Compared with cabazitaxel, the lower costs of radium-223 are driven by lower costs of the drug, administration and adverse events.CONCLUSIONRadium-223 may be a less costly treatment strategy offering similar gains in health benefits compared with abiraterone, cabazitaxel and enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel from the Dutch societal perspective.

44. Evaluation of bone metastatic burden by bone SPECT/CT in metastatic prostate cancer patients: defining threshold value for total bone uptake and assessment in radium-223 treated patients.

Author(s): Umeda, Takuro; Koizumi, Mitsuru; Fukai, Shohei; Miyaji, Noriaki; Motegi, Kazuki; Nakazawa, Shuto; Takiguchi, Tomohiro

Source: Annals of nuclear medicine; Feb 2018; vol. 32 (no. 2); p. 105-113

Publication Date: Feb 2018

Publication Type(s): Journal Article

PubMedID: 29243019

Available at Annals of Nuclear Medicine - from International DOI Foundation

Abstract:OBJECTIVESTo establish a new three-dimensional quantitative evaluation method for bone metastasis, we applied bone single photon emission tomography with computed tomography (SPECT/CT). The total bone uptake (TBU), which measures active bone metastatic burden, was calculated as the sum of [mean uptake obtained as standardized uptake value (SUV) above a cut-off level] × (the volume of the lesion) in the trunk using bone SPECT/CT. We studied the threshold value and utility of TBU in prostate cancer patients treated with radium-223 (Ra-223) therapy.METHODSTo establish the threshold value of TBU, we compared bone metastatic and non-metastatic regions in 61 prostate cancer patients with bone metastasis and 69 without. Five fixed sites in each patient were selected as evaluation points and divided into bone metastatic and non-metastatic sites. Sensitivity and specificity analysis was applied to establish the threshold level. Using the obtained threshold value, we then calculated the TBU in nine prostate cancer patients who received Ra-223 therapy, and compared the results with the bone scan index (BSI) by BONENAVI® and visual

evaluation of bone scintigraphy.RESULTSUptake was significantly lower in non-metastatic sites in patients with bone metastasis than in patients without metastasis. Sensitivity and specificity analysis revealed SUV = 7.0 as the threshold level. There was a discrepancy between TBU and BSI change in two of the nine patients, in whom TBU change correlated with visual judgement, but BSI change did not. In two patients, BSI was nearly 0 throughout the course, but the TBU was positive and changed, although the change was not large. These results suggest that TBU may be more accurate and sensitive than BSI for quantitative evaluation of active bone metastatic burden.CONCLUSIONWe established a threshold value (SUV > 7.0) for three-dimensional TBU for evaluating active bone metastatic burden in prostate cancer patients using bone SPECT/CT. Despite the small number of patients, we expect the change in TBU could be more accurate and sensitive than the change in BSI among patients who received Ra-223.

45. An open-label, multicenter phase 1b trial of radium-223 + paclitaxel in cancer patients with bone metastases: Safety results from the breast cancer patient subgroup

Author(s): Danson S.J.; Perets R.; Lopez J.; Joensuu H.; Peer A.; Harris S.J.; Souza F.; Ploeger B.; Pereira K.M.C.; Geva R.

Source: Cancer Research; Feb 2018; vol. 78 (no. 4)

Publication Date: Feb 2018

Publication Type(s): Conference Abstract

Abstract: Background: Taxanes have an established role in treating breast cancer (BC), and combination with radium-223 (Ra-223) may be an option in patients (pts) with bone metastases. Both therapies impact hematologic parameters, but myelosuppression risk in combination is unknown. A phase 1b trial (NCT02442063) in cancer pts with bone metastases studied Ra-223+paclitaxel (PTX) safety and mode of interaction regarding myelosuppression; BC subgroup safety results are presented. Methods: Eligible pts had a malignant solid tumor with >=2 bone metastases and were PTX candidates. Treatment (tx) was 7 PTX cycles (90 mg/m2/wk IV per local standard of care, 3 wk on/1wk off) + 6 Ra-223 cycles (55 kBq/kg IV; 1 injection q4wk, starting at PTX cycle 2). Primary endpoint was % pts with neutropenia and thrombocytopenia during Ra-223+PTX (cycles 2, 3) vs PTX alone (cycle 1). A dose-exposure-response model describing time course of Ra-223+PTX-induced suppression of absolute neutrophil counts was used to evaluate Ra-223+PTX mode of interaction (additive or synergistic) in the total population. Results: 15/22 enrolled pts were treated (total population); 7 had BC (BC subgroup). Baseline characteristics of the 2 groups were similar; ECOG PS was better in BC pts (Table). Fewer BC pts had prior taxane therapy (29% vs 53%), but rates of >=3 prior chemotherapy regimens were similar (43% vs 47%). BC pts, vs total population, had slightly longer median tx duration for Ra-223 (6 vs 5.5 cycles) and PTX (7 vs 6 cycles), and more pts who completed 6 Ra-223 doses (57% vs 47%). Tx discontinuation related to disease progression in 29% of BC pts vs 33% in total population. Table shows TEAEs. In the BC subgroup, all 7 pts completed cycle 3 and Gr 3 neutropenia rates were 43% in cycle 2 and 14% in cycle 3, vs 29% in cycle 1; there was no Gr 4 neutropenia or Gr 3/4 thrombocytopenia. In the total population, 13 pts completing cycle 3 were in the pharmacodynamics analysis. Their Gr 3 neutropenia rates were 31% in cycle 2 and 8% in cycle 3, vs 23% in cycle 1; there was no Gr 4 neutropenia or Gr 3/4 thrombocytopenia. Myelosuppression model for the total population showed an additive effect of Ra-223 to PTX-induced neutropenia, with an additional 10% average decrease in absolute neutrophil count vs PTX alone. BC subgroup modeling was not feasible due to small sample size. (Table presented) Conclusions: Ra-223 was well tolerated when combined with PTX in pts with solid tumors and bone metastases. The BC subgroup vs total population had slightly higher hematologic AE rates, but fewer Gr 3/4 and serious TEAEs; more BC pts also completed study tx. The combination should be explored further in pts with bone metastases.

46. Phase II study of the feasibility and safety of radium-223 dichloride in combination with hormonal therapy and denosumab for the treatment of patients with hormone receptor-positive breast cancer with bone-dominant metastasis

Author(s): Tahara R.K.; Fujii T.; Saigal B.; Ibrahim N.K.; Damodaran S.; Barcenas C.H.; Murray J.L.; Chasen B.A.; Shen Y.; Liu D.D.; Hortobagyi G.N.; Tripathy D.; Ueno N.T.

Source: Cancer Research; Feb 2018; vol. 78 (no. 4)

Publication Date: Feb 2018

Publication Type(s): Conference Abstract

Abstract: Background: Radium-223 dichloride (Ra-223) is a therapeutic alpha particle-emitting radiopharmaceutical compound which have antitumor effect targeted on bone metastases. Alpha particles induces double strand DNA breaks and localized cytotoxic effect to cancer cells with limiting harm on normal tissues. We are conducting a phase II clinical trial of combination of Ra-223, hormonal therapy, and denosumab treatment in patients with hormone receptor (HR)-positive bone-dominant metastatic breast cancer (NCT02366130). In this preliminary analysis of the study, we aimed to evaluate the feasibility and safety of this combination therapy. Methods: This single-center phase II study seeks to determine the efficacy and safety of Ra-223 in combination with hormonal therapy and denosumab. Major eligibility criteria include HR-positive breast cancer with bone and/or marrow predominant metastases. Patients with two or more visceral metastases were not eligible. There was no limit in the number of prior hormonal therapies in the metastatic setting. Patients received Ra-223 injection (55 kBq/kg intravenously) on day 1 of the study and then every 4 weeks thereafter for 6 cycles. Patients were also administered a single hormonal agent (i.e., tamoxifen, aromatase inhibitor, or fulvestrant at standard doses) daily and denosumab (120 mg subcutaneously) every 4 weeks. For this analysis, adverse events (AEs) were summarized using descriptive statistics. Results: A total of 25 patients were enrolled and 22 were evaluable between March 2015 and December 2016. Median age was 58.5 years (range 31-79), and 59% of patients were postmenopausal. ECOG performance status was 0 in 16 patients (73%), and 1 in six patients (27%). HER2/neu was positive in only one patient. Four patients (18%) were de novo metastasis, no patients had visceral metastasis, and multiple bone metastases in 20 patients (91%) vs. focal metastasis in 2 (9%). Median time from diagnosis of bone metastasis was 4.8 months (range 0.5-96.6). Prior therapy for metastatic disease consisted of hormonal therapy in 50% of the patients (eight patients with one line and three patients with two lines), chemotherapy (9%), palbociclib (14%), radiation to bone metastasis (50%), and bone-supportive therapy (27% with zoledronic acid, 27% with denosumab). The median number of cycles of Ra-223 administered was 6 (range 4-6). The median follow-up time was 4 months (range 2-8). There were no grade 3 or 4 AEs. Major non-hematological grade 1 and 2 AEs were bone pain (77%), fatigue (45%), nausea (36%), diarrhea (32%), AST/ALT elevation (23%), hot flashes (23%), and headache (18%). The most common hematological AEs were grade 1 or 2 neutropenia (23%), anemia (14%), and thrombocytopenia (18%). There was no treatment delay or discontinuation due to AEs. Conclusion: Our results suggest that the addition of Ra-223 to hormonal therapy and denosumab is a feasible and safe combination therapy in patients with HR-positive breast cancer with bone-dominant metastasis. We continue to enroll patients in the phase II trial to evaluate the efficacy of the treatment.

47. Radium-223 international early access program: results from the Spanish subset.

Author(s): Carles, Joan; Méndez, Mª José; Pinto, Álvaro; Sáez, Mª Isabel; Arranz, José A; Maroto, Pablo; López-Criado, Pilar; Mellado, Begoña; Donas, Jesús García; Hernando, Susana; León, Luís; Del Alba, Aránzazu González; Laínez, Núria; Esteban, Emilio; Reynés, Gaspar; Pérez-Gracia, José L;

Germà, Josep R; López-Brea, Marta; Pérez-Valderrama, Begoña; Moretones, Cristina; Castellano, Daniel

Source: Future oncology (London, England); Jan 2018; vol. 14 (no. 1); p. 41-50

Publication Date: Jan 2018

Publication Type(s): Journal Article

PubMedID: 29232987

Abstract:AIMTo report results from the Spanish subset included in the radium-223 international early access program (iEAP).PATIENTS & METHODSNinety patients with castration-resistant prostate cancer and bone metastases received radium-223 55 kBq/kg every 4 weeks for six cycles.RESULTSThe median time to disease progression was 8 months and to prostate-specific antigen progression was 4 months. The percentage of patients with ≥50% confirmed declines in prostate-specific antigen was 9%. The median overall survival was 14 months. Grade 3 or 4 treatment emergent adverse events (TEAEs) occurred in 34% of patients (serious TEAEs 28%, TEAEs leading to discontinuation 27%).CONCLUSIONOutcomes of the Spanish subset are consistent with the iEAP. Radium-223 was generally well tolerated with no safety concerns.

48. Impact of treatment delay in Radium-223 therapy of metastatic castration-resistant prostate cancer patients.

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Source: Annals of nuclear medicine; Jan 2018; vol. 32 (no. 1); p. 16-21

Publication Date: Jan 2018

Publication Type(s): Journal Article

PubMedID: 28975586

Abstract:BACKGROUNDRadium-223-dichloride (Ra-223) is an alpha-emitting, bone seeking radionuclide therapy approved for patients with metastatic castration-resistant prostate cancer (mCRPC). In the fall of 2014, a global temporary shortage of Ra-223 occurred for 2 months due to production irregularities. The aim of this study was to assess whether prolonged interval between Ra-223 cycles to non-disease related causes had a negative impact on clinical outcome of therapy.MATERIALS AND METHODSRetrospective single-center study of mCRPC patients who initiated Ra-223 therapy in the period from March 2014 to February 2015. End points were number of completed Ra-223 cycles, overall survival (OS) and radiographic progression-free survival (rPFS). Bone scintigraphy, CT of thorax and abdomen, hematological status, PSA and alkaline phosphatase were evaluated prior to first dose and after 3rd and 6th treatment, respectively. Follow-up period was 18 months after first Ra-223 cycle.RESULTSA total of 50 consecutive patients initiated Ra-223 therapy in the time period. Seventeen of 50 patients (34%) had prolonged interval between cycles due to delivery problems. Median delay was 4 weeks (range 3-9 weeks). Patients with delayed treatment had significantly longer median rPFS [delayed patients: 7.1 months (95% CI 4.9-9.3) vs. 4.5 months (95% CI 2.8-6.3)]. There was no significant difference in number of completed cycles or median OS.CONCLUSIONWe find no negative impact of prolonged interval between Ra-223 cycles due to non-disease related reasons on OS, rPFS or number of completed treatment cycles.

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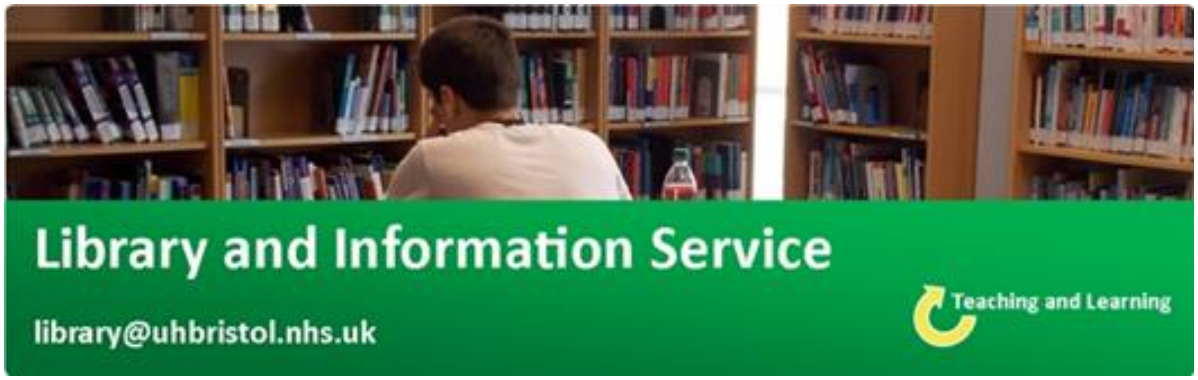

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